PHD

Synthesis in the shikimate area

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SYNTHESIS IN THE SHIKIMATE AREA

Submitted by

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for the degree of Ph.D.

of the University of Bath

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Dedicated to my Mother and Father

for their love and support.

ACKNOWLEDGEMENTS

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ABSTRACT

The shikimate pathway is the major biosynthetic route by which plants and micro-organisms produce the aromatic amino acids and a plethora of other natural products. The details of the pathway are discussed in Chapter 1, together with a review of the recent syntheses of shikimic acid and of later intermediates in the shikimate pathway.

Our synthesis of analogues of shikimic acid, which are of interest as potential enzyme inhibitors, is described in Chapter 2. Starting from shikimic acid, two routes to our α-methylene lactone are discussed as well as a route to the β-methylene lactone. Simple protective steps followed by the subsequent bromination at C-5 to give the 5α-bromoshikimate then treatment with an allyl stannane prepared from methyl methacrylate gave us the required "carba-chain" at C-5. The second route involves the use of Berchtold's epoxide[59] to generate 5β-iodoshikimate and 5β-bromoshikimate which are then reacted with the allylstannane to give the α and β lactones.

Full experimental details for the preparation of these compounds are given in Chapter 3.

ABBREVIATIONS

Ac	acetyl
ACN	azobis(cyclohexone carbonitrile)
AcOH	acetic acid
ADP	adenosine diphosphate
AIBN	azobis(isobutyronitrile)
aq	aqueous
ATP	adenosine triphosphate
$BF_3.Et_2O$	boron trifluoride etherate
Boc	*tert*-butoxycarbonyl
Bn	benzyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
cat.	catalytic
C.I.	chemical ionisation
conc.	concentrated
δ	deformation
DAHP	3-deoxy-D-arabinoheptulosonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarisation Transfer
DHQ	dehydroquinate
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2[1H]-pyrimidinone

DMSO	dimethylsulfoxide
E.I.	electronic ionisation
5-EPS	5-enolpyruvylshikimate
5-EPS-3-P	5-enolpyruvylshikimate-3-phosphate
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
F.A.B.	fast atomic bombardment
HMPA	hexamethylphosphoramide
hr	hour
^{i}Pr	isopropyl
i.r.	infrared spectroscopy
KO^{t}Bu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
lit.	literature
LUMO	lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
MeOH	methanol
min	minute
m.p.	melting point
m.s.	mass spectroscopy
Ms	methanesulphonyl mesyl
NAD^{+}, NADH	nicotinamide adenine dinucleotide, reduced form
$NADP^{+}$, NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide

n.m.r.	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulphonyl
PCC	pyridinium chlorochromate
PEP	phosphoenol pyruvate
Ph	phenyl
Ⓟ	phosphate, PO_3^{2-}
PPTS	pyridinium *p*-toluenesulphonate
Pr	propyl
p-TSA	*para*-toluenesulfonic acid
py	pyridine
R_F	retention factor
RT	room temperature
S_N1	substitution nucleophilic unimolecular
S_N2	substitution nucleophilic bimolecular
SOMO	singularly occupied molecular orbital
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilane
Tf	trifluoromethanesulfonate (triflic)
THF	tetrahydrofuran
TFA	trifluoroacetic acid
Ts	*p*-toluenesulphonyl (tosyl)
T.l.c.	thin layer chromatography
TMS	trimethylsilyl (or trimethylsilane as n.m.r. standard)
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	tolyl

For spectral data:

n.m.r.

s	singlet
d	doublet
t	triplet
q	quartet
pent	pentet
m	multiplet
brd	broad
J	coupling constant (Hz)
Ar	aryl

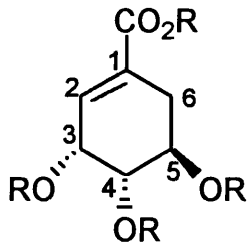
i.r.

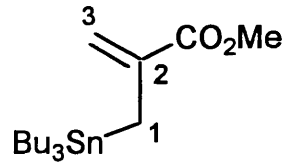
s	strong
m	medium
w	weak

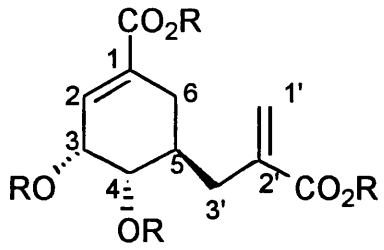
NOMENCLATURE

The nomenclature of cyclohexene and cyclohexane compounds referred to in this thesis, is based on shikimic acid nomenclature, even though this may not necessarily conform to IUPAC convention. This permits analysis of any compound without reference to the nomenclature for that particular compound, and furthermore, allows direct comparison of NMR data.

The numbering system employed labels the carboxylate substituted carbon as C-1 and proceeds anticlockwise around the ring, through the double bond. More highly substituted derivatives are named as depicted below. All other compounds are named in accordance with IUPAC rules.







CONTENTS

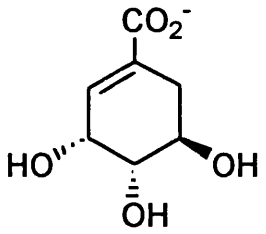
CHAPTER ONE

INTRODUCTION

1.1 The ShikimatePathway

1.1.1 Introduction

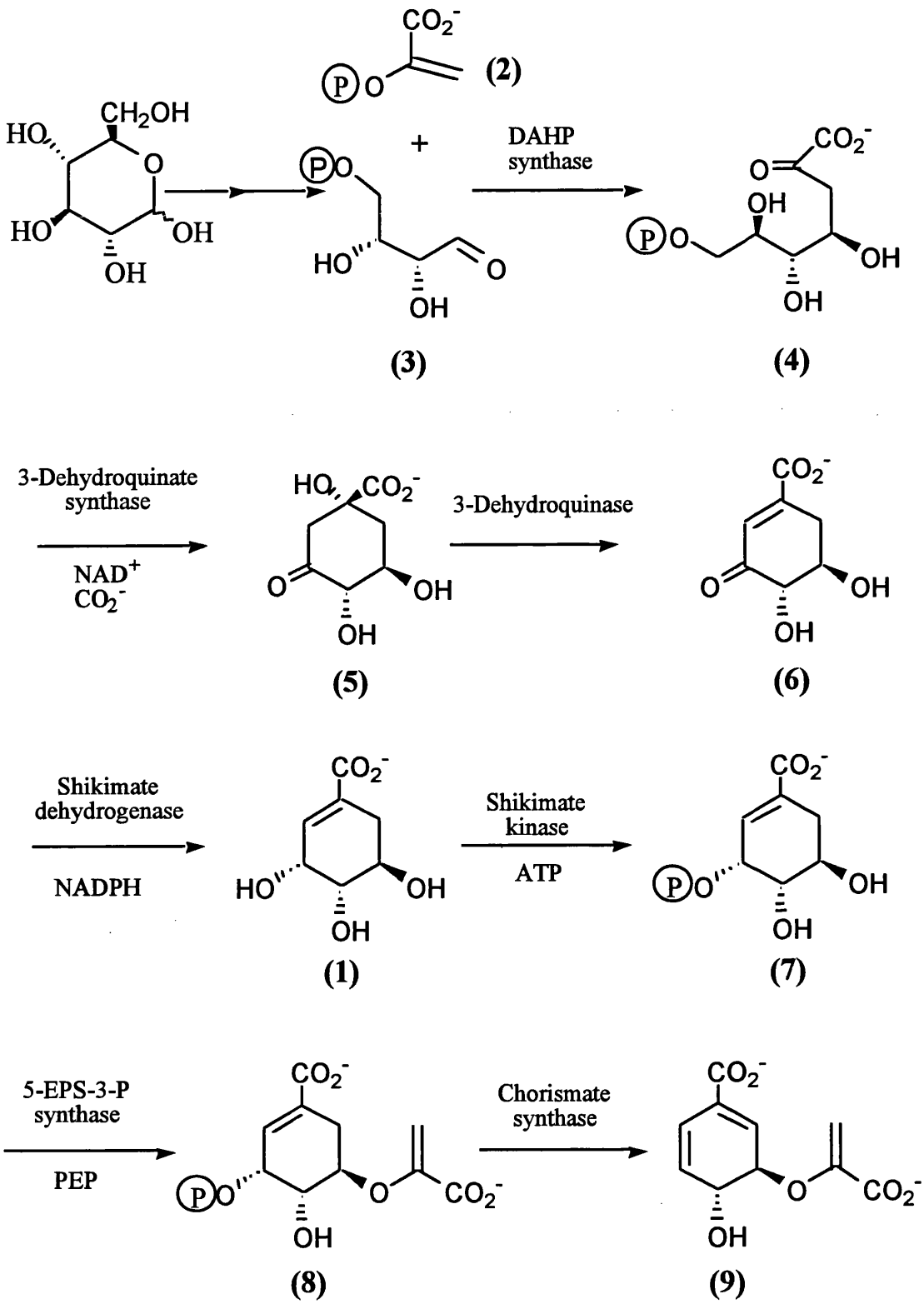
The glucose-derived shikimate pathway and the acetate-derived polyketide pathway are major routes for the biosynthesis of aromatic compounds in plants, fungi and micro-organisms.[1] The former leads to the formation of the aromatic amino acids, L-phenylalanine, L-tryptophan and L-tyrosine, and is named after a key intermediate, shikimic acid **1**.



1

This was first isolated from the fruit of *Illicium religiosum* in 1885 by Eykmann.[2] The name for this compound is derived from the Japanese name for this plant, *shikimi-no-ki*. Work by Fischer and Dangschat[3], Karrer[4] and Freudenberg[5], proved the structure and absolute stereochemistry, but the true importance of shikimic acid was not fully appreciated until work by Davis[6] in the 1950's.

Davis showed that certain mutants of *Escherichia coli* and *Aerobacter aerogenes* accumulated shikimic acid, while other mutants, blocked at a different point in the pathway, were able to replace missing aromatic substrates by utilizing



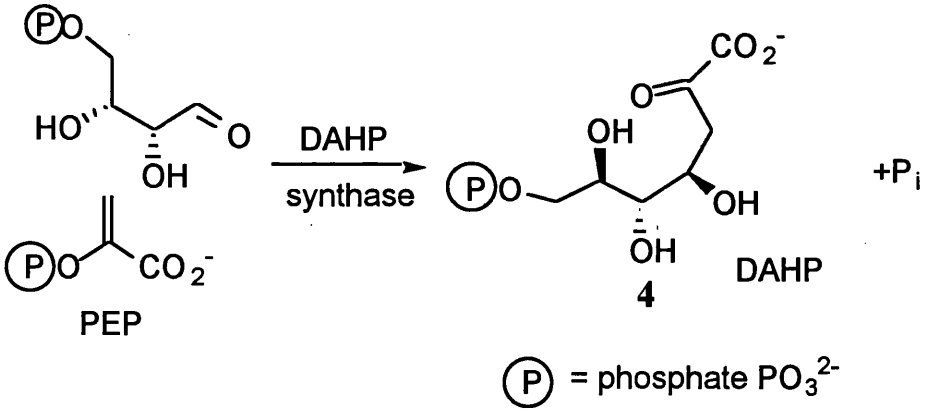
Scheme 1.1 The Common Pathway

shikimic acid. These observations identified shikimic acid as a common precursor for each of the aromatic compounds cited above together with *p*-aminobenzoic acid and *p*-hydroxybenzoic acid. Further observations by Davis, Sprinson[7], Gibson[8] and subsequent workers revealed the common pathway to involve eight intermediates, leading from glucose to shikimic acid and then to chorismic acid (**Scheme 1.1**).

1.1.2 The Common Pathway

The main part of the pathway from D-glucose to chorismate **9** is known as the common pathway. The precise mechanism for each stage remains debatable although the intermediates have all been identified.

Thus, oxidation of glucose by the pentose phosphate pathway affords D-erythrose-4-phosphate **3**, and by glycolysis affords phosphoenolpyruvate (PEP, **2**). The enzyme [7-phospho-2-keto-3-deoxy-*D-arabino*-D-erythrose-4-phosphate lyase (pyruvate phosphorylating), E.C.4.2.1.15][1f] catalyses the condensation of phosphoenolpyruvate and D-erythrose-4-phosphate to give 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP) **4** and inorganic phosphate. This is the first committed step in the shikimate pathway, the enzyme more conveniently being referred to as DAHP synthase (**scheme 1.2**).

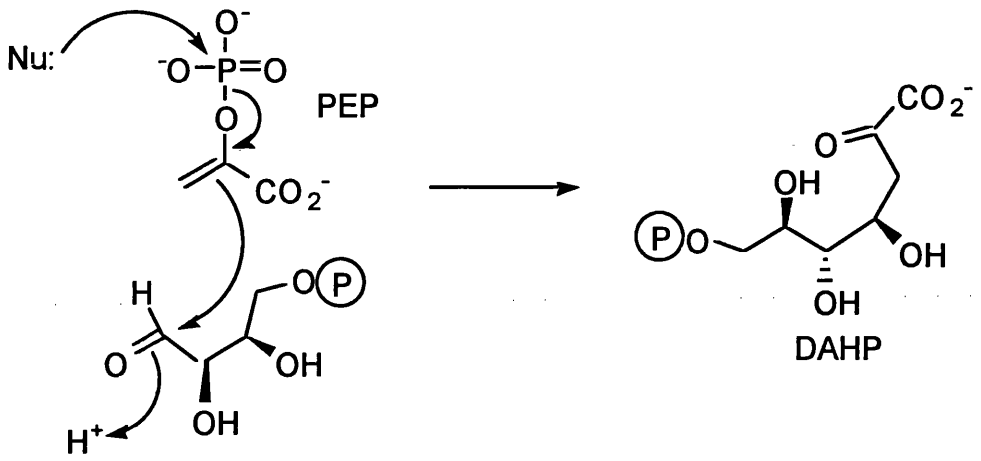


Scheme 1.2

Originally the mechanism of the DAHP synthase reaction, proposed by Sprinson *et al.*[9], was thought to involve a concerted process in which nucleophilic attack at the phosphorus atom of PEP results in a cleavage of the P-O bond. This

cleavage generates a reactive enol pyruvate anion which rapidly adds to D-erythrose-4-phosphate (**scheme 1.3**).

However, later kinetic studies[10], pointed to a 'ping-pong' mechanism in which one of the reaction products is released before both substrates can bind to the



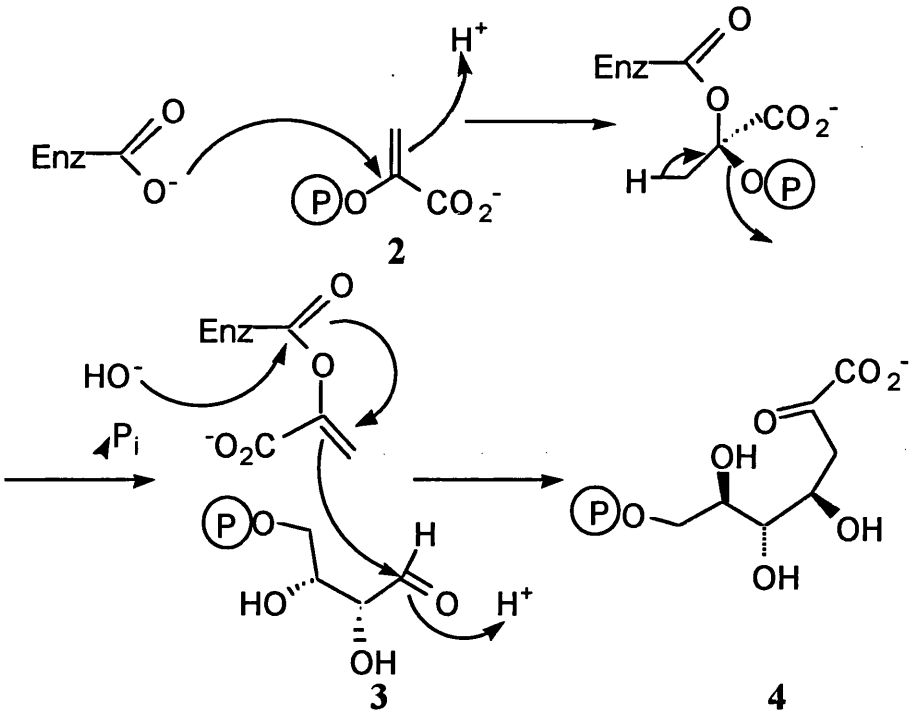
Scheme 1. 3 Original postulated mechanism for DAHP synthase

enzyme. Since PEP tends to stabilise the enzyme against denaturation[11], it seemed logical to postulate that an enzyme bound enolpyruvate intermediate is formed concurrently as a release of inorganic phosphate.

Experiments[10,12] in which the enol oxygen atom of PEP was labelled with ^{18}O showed that it is the C-O bond, and not the P-O bond, that is broken. An alternative mechanism was thus proposed in which the substrate PEP is first transferred to a nucleophilic group on the enzyme, such as a carboxyl group (**scheme 1.4**). Elimination of a phosphate ion leaves an enolpyruvyl enzyme complex, which undergoes acyl-oxygen cleavage and initiates an aldol condensation with D-erythrose-4-phosphate.

The ring closure of DAHP to give dehydroquinate (DHQ, **5**), the first of the carbocyclic metabolites in the common pathway, is catalysed by the enzyme 7-phospho-3-deoxy-*D-arabino*-heptulosonate phosphate lyase, which is more

commonly known as 3-dehydroquinate synthase. The enzyme requires NAD^{+}[13] and a divalent metal cation. Mechanistic studies use Co^{2+} as the cation whereas Zn^{2+} is



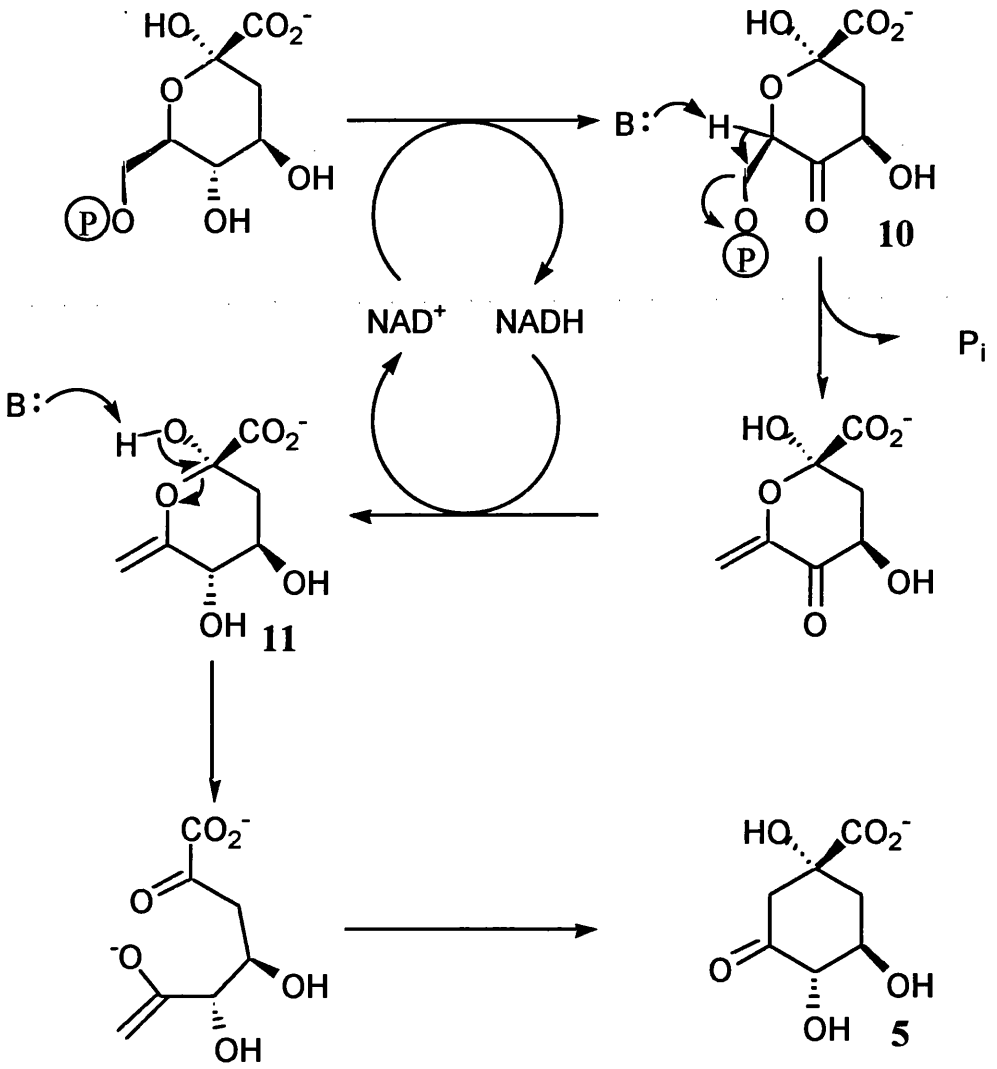
Scheme 1.4 Postulated 'Ping-Pong' mechanism for DAHP synthase

more likely in *vivo*. Mechanisms for the sequence of reactions which this enzyme undergoes has been postulated by Sprinson[13] (**Scheme 1.5**). The NAD^{+} to NADH mediated oxidation at C-5 acidifies the C-6 proton which facilitates the phosphate anion to β-eliminate. The enzyme-bound NADH then reduces the ketone to give the enol pyranose **11** which, after ring opening, undergoes an intramolecular aldol reaction to give 3-dehydroquinate **5**.

This sequence of reactions, converting DAHP to 3-dehydroquinate, is particularly complex for a single monomeric enzyme. The enzyme, presumably having only a single active site, seems to act as a dehydrogenase, a phospholypase, a pyranose-opening enzyme and as an internal aldolase[14].

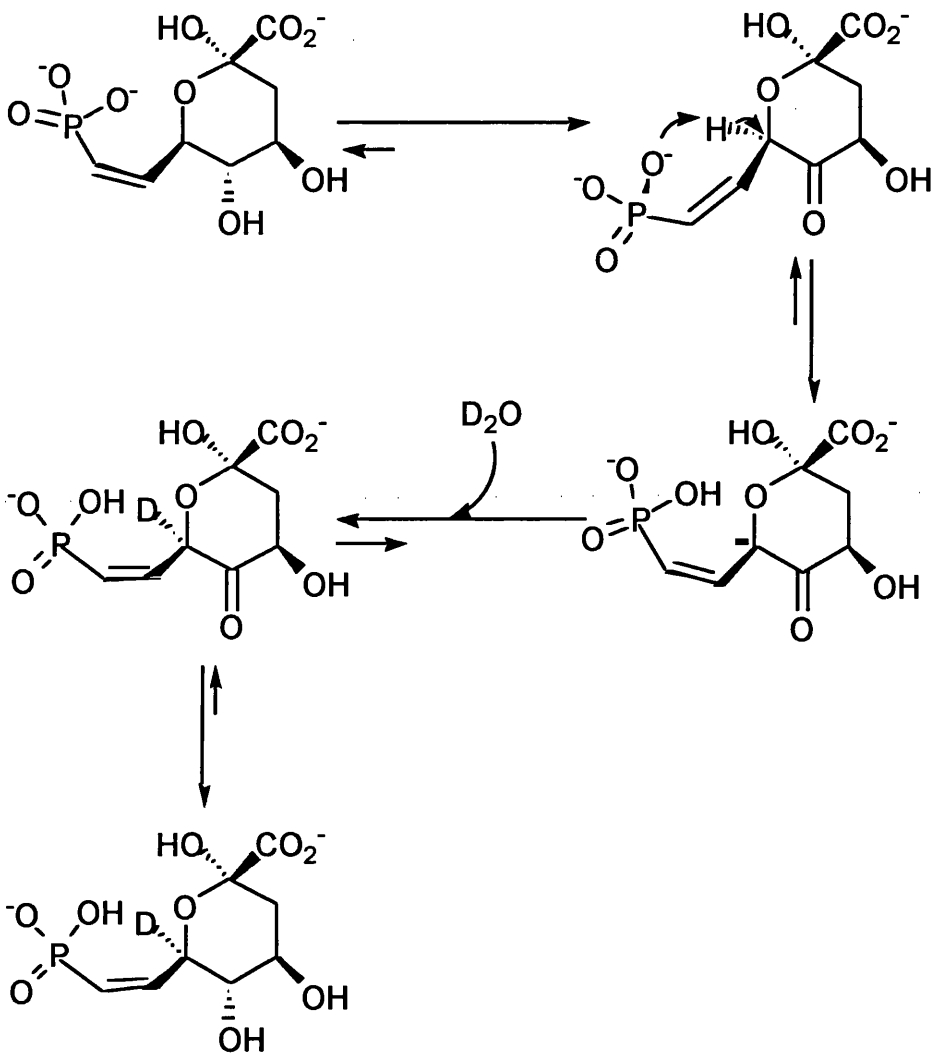
Knowles[14] showed that the enzyme was not directly responsible for the E1cB elimination of phosphate after the initial oxidation of DAHP. He argued that as

long as the substrate is bound to the enzyme in a suitable conformation, then one of the phosphoryl oxygens can abstract the C-6 proton (**scheme 1.6**). Inexorably, elimination then follows.



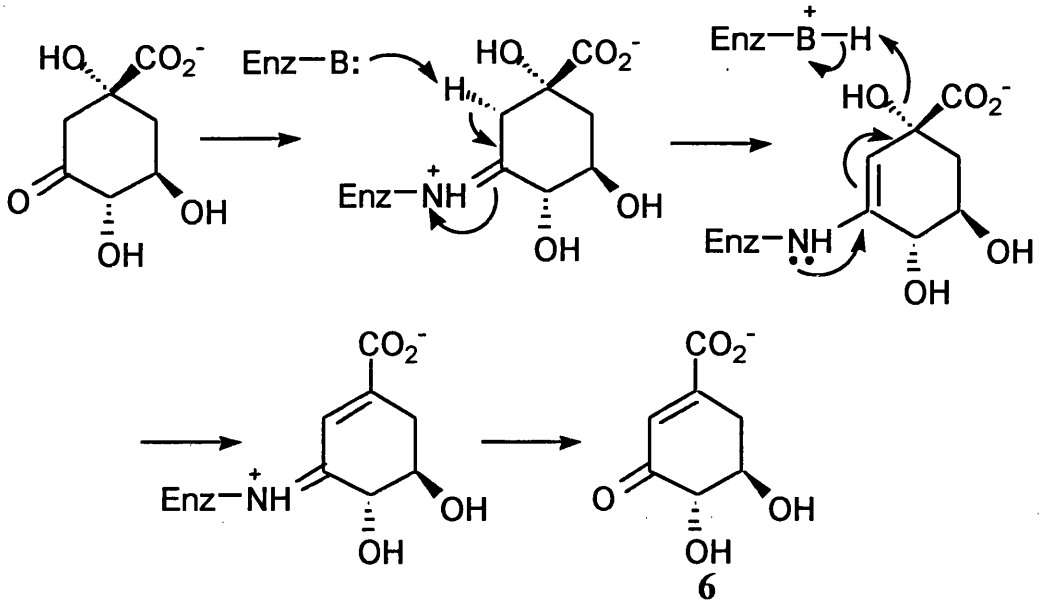
Scheme 1.5

Bartlett has synthesised the enol pyranose intermediate (**10**)[15] . Removal of the o-nitrobenzyl ketal, by photolysis in neutral aqueous solution, gave complete spontaneous conversion to 3-dehydroquinate. This, along with the work done by Knowles, suggests that the enzyme is actually only a dehydrogenase.



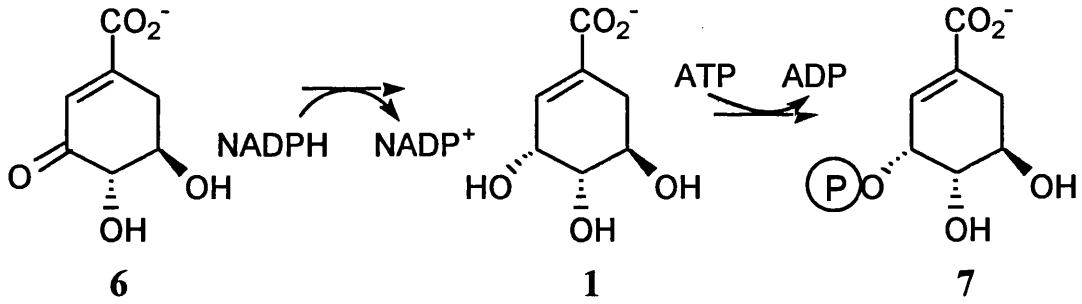
Scheme 1.6

3-Dehydroquinase catalyses the dehydration of 3-dehydroquinate (**5**) to dehydroshikimate (**6**) (**scheme 1.7**), and labelling experiments by Haslam[16] show that the loss of water proceeds in a stereospecific *cis* fashion. In order to account for this it has been proposed[17] that a histidine residue in the active site facilitates the *syn* elimination process, possibly *via* an iminium salt. Certainly a lysine residue in the active site is known to form a Schiff's base with the oxo group of the 3-dehydroquinate.



Scheme 1.7

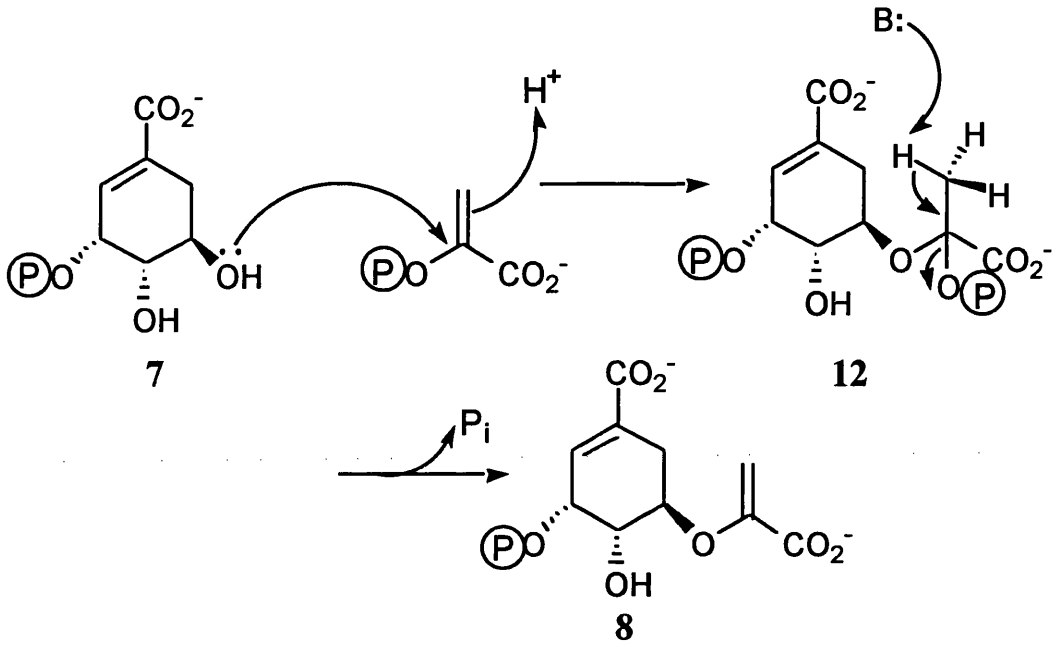
Shikimate dehydrogenase catalyses the reversible reduction of dehydroshikimic acid **6**, in the presence of NADPH, to give shikimic acid **1**. Shikimate kinase then catalyses the phosphate transfer from ATP to the hydroxyl group at C-3 of shikimic acid to give shikimic acid-3-phosphate **7(scheme 1.8)**.



Scheme 1.8

The enzyme that catalyses the biochemically remarkable reaction of PEP and shikimate 3-phosphate is phosphoenolpyruvate:3-phosphoshikimate 5-O-(1-carboxyvinyl)transferase, commonly known as 5-enolpyruvylshikimate-3-phosphate synthase (5-EPS-3-P synthase). Initial studies on the enzyme were carried out by

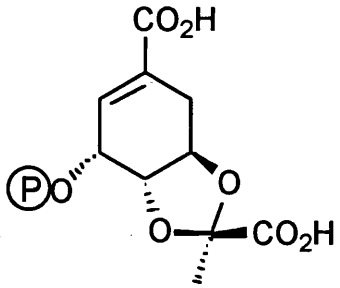
Levin and Sprinson who proposed that it exerts the effect through an addition-elimination mechanism[18] (**scheme 1.9**).



Scheme 1.9

Abeles *et al.*[19] propose a mechanism in which an enzyme:PEP complex analogous to that proposed for the transferase, is formed (**scheme 1.10**). This mechanism was based upon analogies to the behaviour of the enzyme UDP-N-acetylglucosamine enolpyruvyltransferase which catalyses the first step in the biosynthesis of the cell wall peptidoglycan. These workers argued that the C-5 hydroxyl group of shikimate 3-phosphate does not initially form a complex with PEP, but combines with an enzymically activated form of this intermediate. However more recent kinetic studies and the isolation of the intermediate **12**[20-24], have lead to a mechanism nearly resembling that outlined by Sprinson. Indeed, Anderson[20] has isolated the tetrahedral intermediate **12**. This is stable under basic conditions, but under acidic conditions it decomposes to give PEP and shikimate 3-phosphate. It is concluded that **12** is a true intermediate on the pathway and that the reaction does proceed by an addition-elimination mechanism involving nucleophilic attack of the C-5 hydroxyl group of shikimate 3-phosphate at C-2 of PEP. Although the intermediate has been characterised, the absolute stereochemistry of the tetrahedral

centre has yet to be determined. NMR studies have been carried out on the intermediate by labelling PEP with ^{13}C at C-2 or C-3 and using this substrate in place of natural PEP.[25] Evans[23] has isolated another tetrahedral intermediate, which is clearly not on the reaction pathway which gives 5-EPS-3-P.[26] This seems to be responsible for the novel shikimate ketal **13** which has been isolated by Sammons[21].



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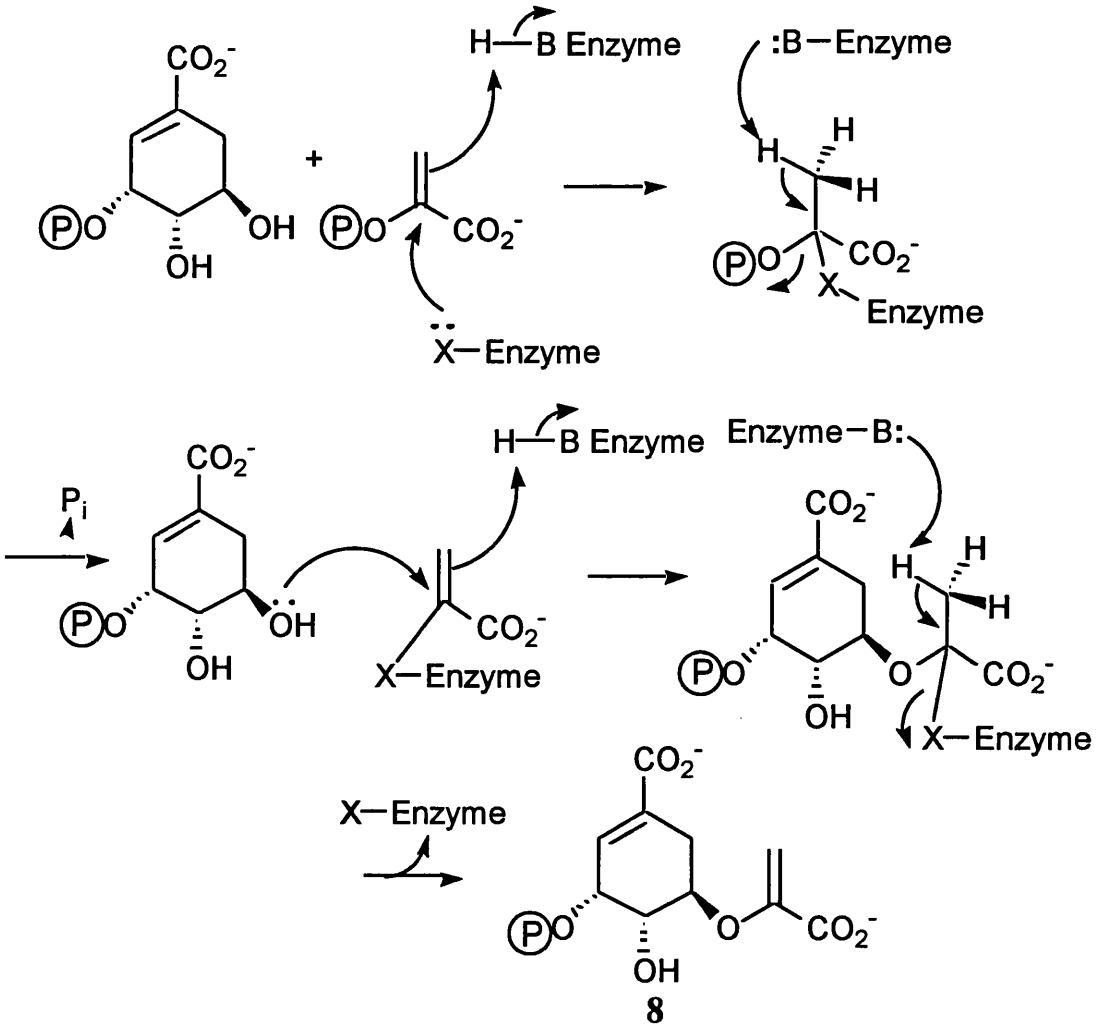
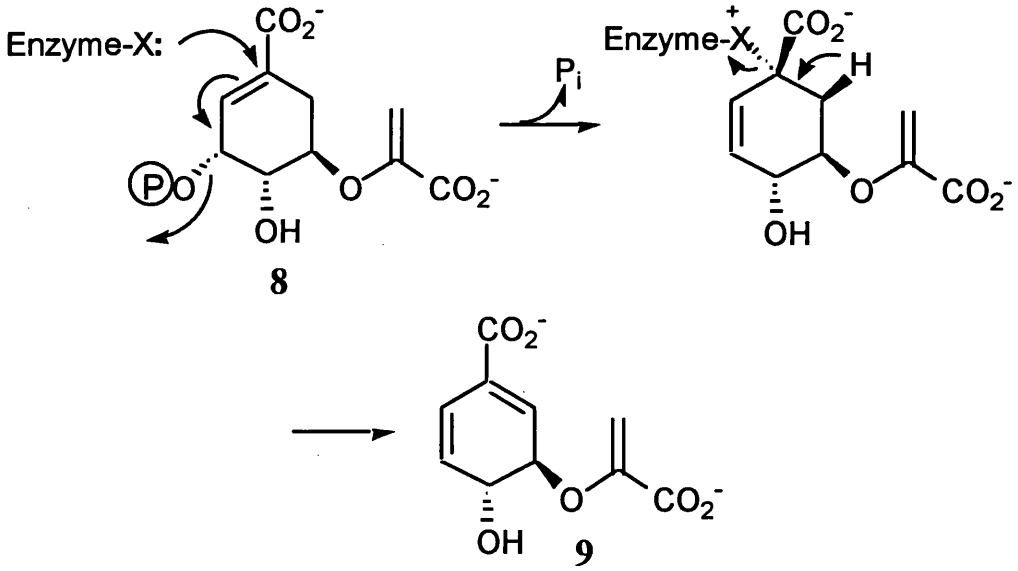


8

Scheme 1.10

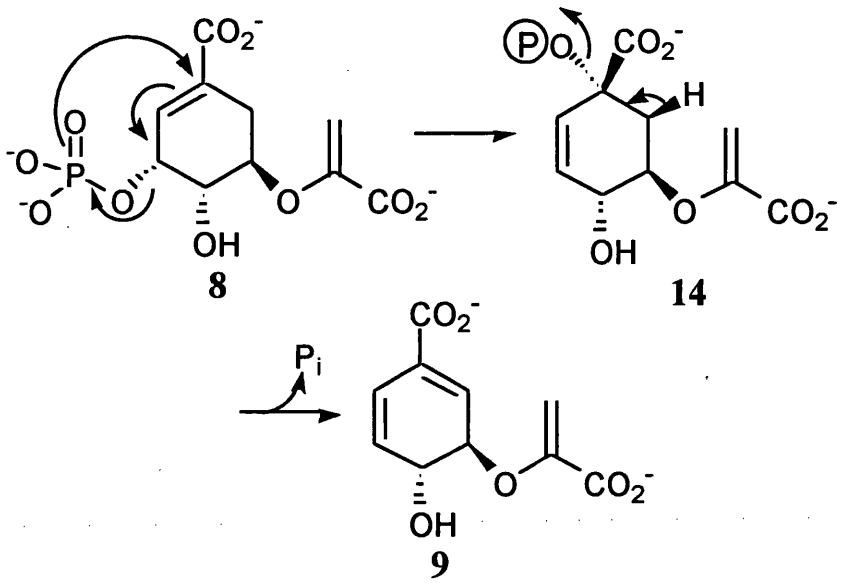
Chorismic synthase [O^5-(1-carboxyvinyl)-3-phosphoshikimate phosphate lyase] catalyses the conversion of 5-EPS-3-P 8 into chorismic acid **9**; the final step in the common pathway. It requires a reduced flavin cofactor, although the reaction results in no net overall change in redox state. Labelling[27,28] experiments have shown that only the 6-*pro*-R hydrogen is lost and thus the overall transformation is a *trans*-1,4-elimination. In cyclohexene systems, concerted 1,4-eliminations proceed predominantly in a *cis* fashion, therefore mechanisms involving a 2 stage process have been proposed. It is possible, however, that the enzyme causes the substrate to adopt a suitable conformation such that a concerted *trans* 1,4-elimination is possible.

A two-stage mechanism, in which an 'X-group' on the enzyme participates has been proposed by Floss[29], and might account for the overall *trans*-elimination (**scheme 1.11**).



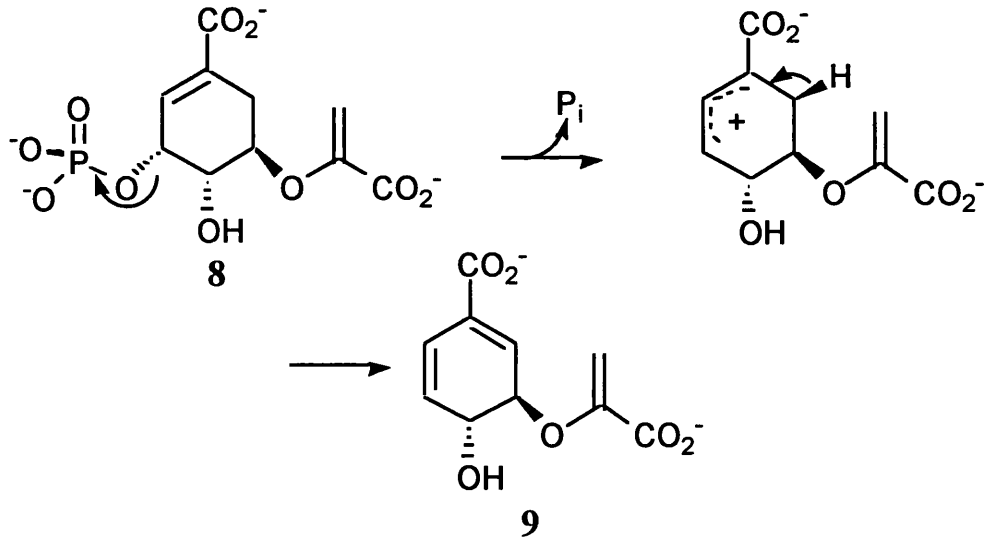
Scheme 1.11

An interesting alternative proposed by Ganem[1b] involves a suprafacial 3,3-rearrangement of **8** to the allylic isomer *iso*-EPSP **14**, followed by *trans*-1,2-elimination (**scheme 1.12**). However, *iso*-EPSP was synthesised by Bartlett[30] and was shown not to be converted to chorismate by chorismate synthase, thus suggesting that *iso*-EPSP is not an intermediate in the reaction pathway.



Scheme 1.12

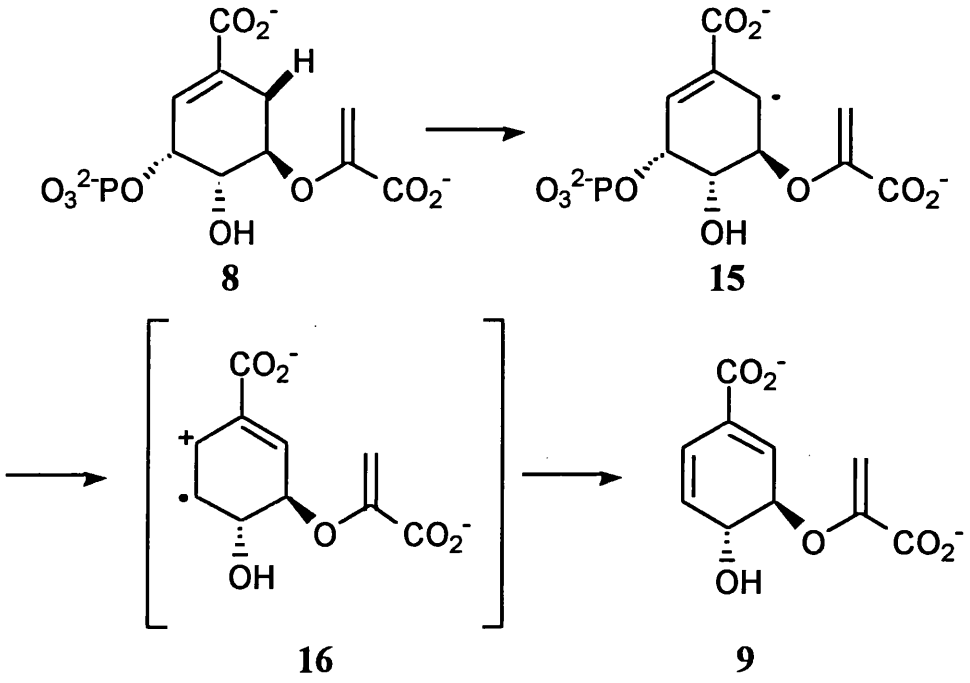
Another possible mechanism involves a carbocation where the phosphate ester group is lost before the loss of the hydrogen at C-6 (**scheme 1.13**).



Scheme 1.13

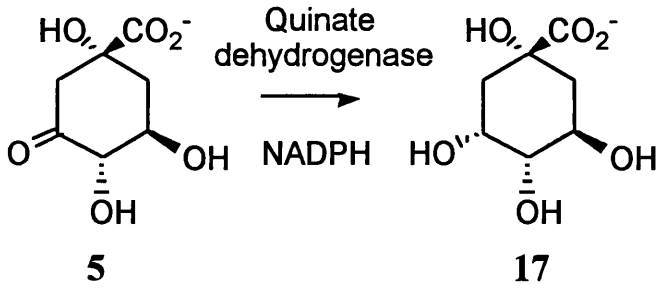
Recently, Bartlett proposed a radical mechanism where abstraction of a hydrogen atom from C-6 first occurs to give an allyl radical **15** (**scheme 1.14**).[31] Heterolytic cleavage of the phosphate group gives the radical cation **16**, which upon single electron transfer affords chorismate. A radical mechanism provides an

explanation for the initial reduction of the enzyme and the requirement of a flavin cofactor.



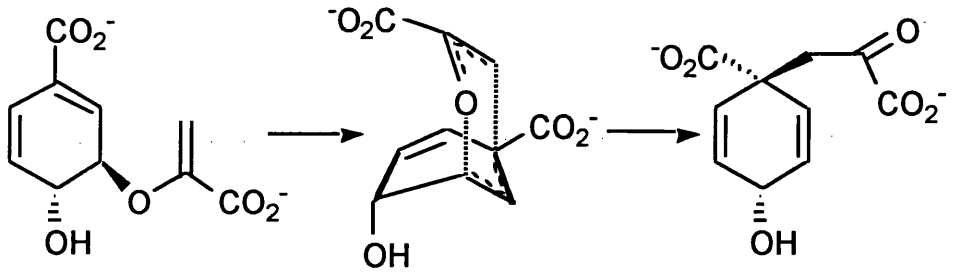
Scheme 1.14

Quinic acid **17**, is widely found in the plant kingdom and is formed by an off-shoot of the common pathway. Once formed, by the reduction of 3-dehydroquinate **5** by NADPH, a reaction which is catalysed by quinate dehydrogenase (**scheme 1.15**), it is not easily metabolised again. However some micro-organisms are able to convert quinic acid into 3-dehydroquinate and thus metabolise the former as an alternate carbon source.



Scheme 1.15

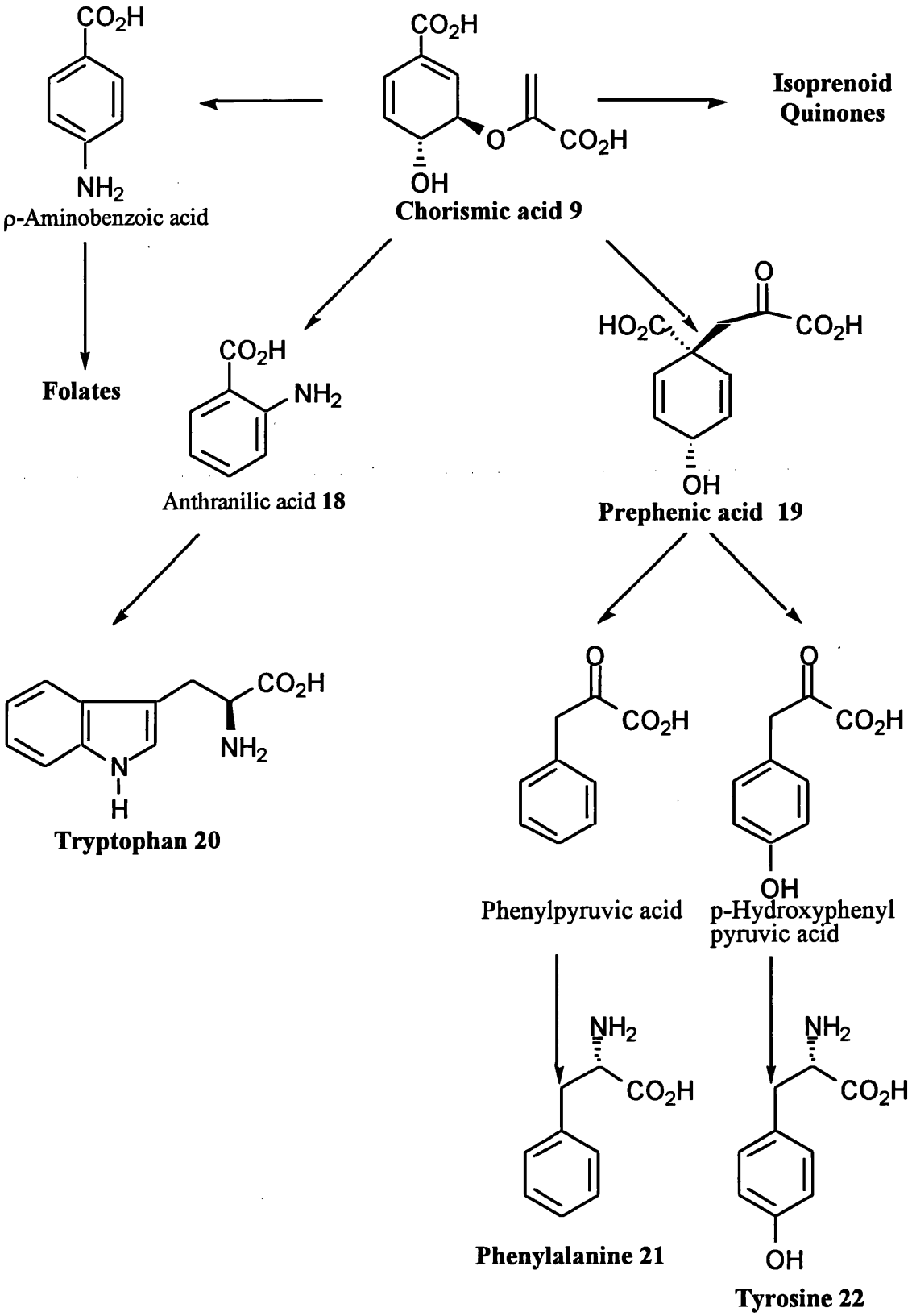
Chorismic acid is the branch point at which the common pathway diverges to give the aromatic amino acids and diverse other compounds (**Scheme 1.16**). Amination of chorismic acid leads through anthranilic acid to tryptophan **20**. The other two aromatic amino acids phenylalanine **21** and tyrosine **22**, are formed *via* rearrangement of chorismic acid to prephenic acid **19**, in what is formally at least, a Claisen rearrangement. This is a unique reaction in biosynthesis, and has been proved to proceed through a chair-like transition state (**scheme 1.17**).[32]



9 **19**

Scheme 1.17

Another route from chorismic acid leads *via* *p*-aminobenzoic acid to the folate group of coenzymes. The isoprenoid quinones which participate in electron transport and oxidative phosphorylation are also derived from chorismic acid.


CO2H
NH2
ρ-Aminobenzoic acid
CO2H
O
CO2H
OH
Chorismic acid 9
Isoprenoid
Quinones
Folates
CO2H
NH2
Anthranilic acid 18
HO2C
O
CO2H
OH
Prephenic acid 19
CO2H
NH2
N
H
Tryptophan 20
O
CO2H
Phenylpyruvic acid
O
CO2H
OH
p-Hydroxyphenyl
pyruvic acid
NH2
CO2H
Phenylalanine 21
NH2
CO2H
OH
Tyrosine 22

Scheme 1.16

1.2 Synthesis of Shikimic acid

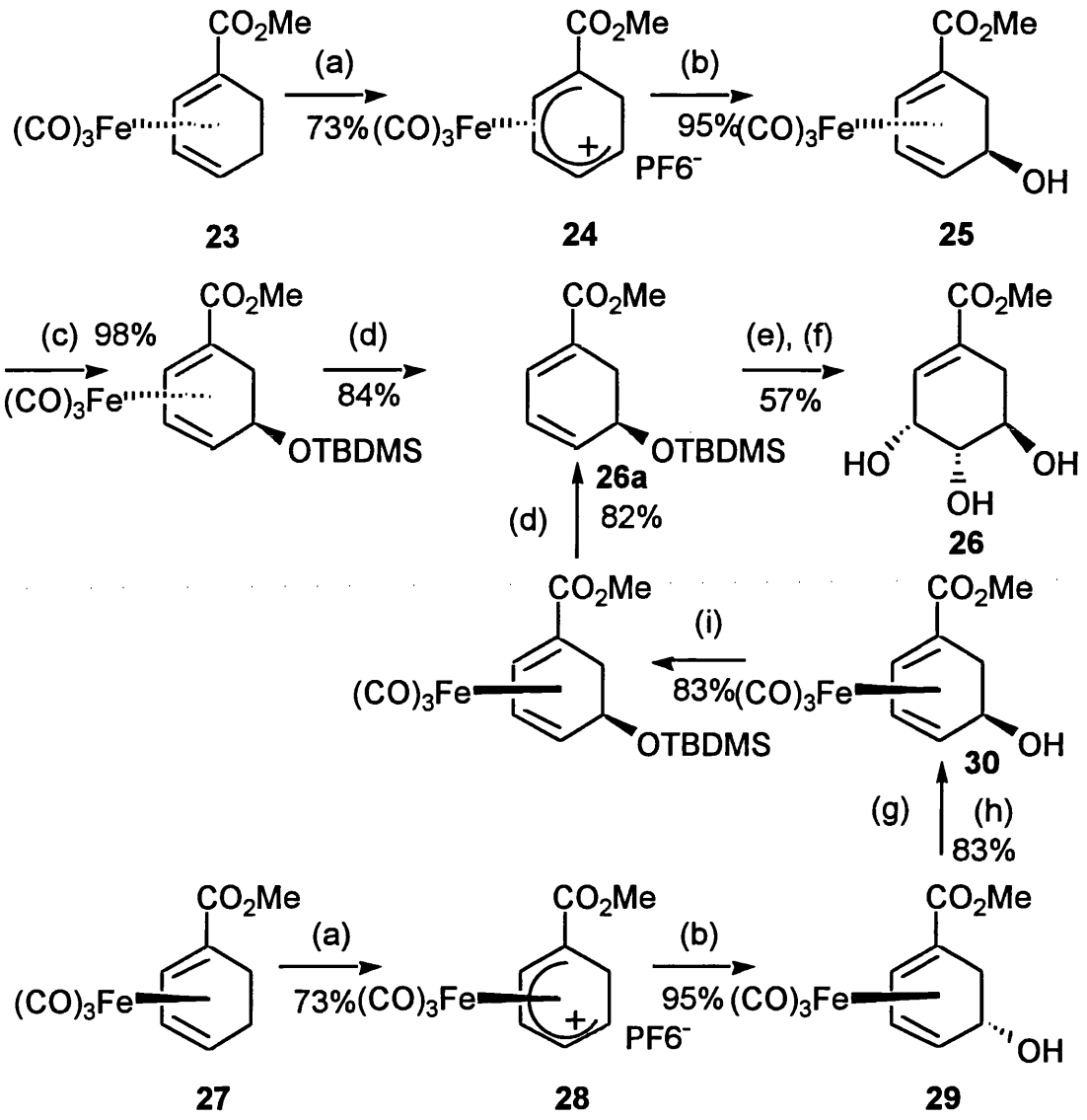
Much has already been published regarding the synthesis of shikimic acid and its structural variants. Such compounds offer the prospect of selective and useful biological activity. For example, the shikimate pathway only occurs in plants and microorganisms. The three aromatic amino acids obtained from the biosynthetic pathway cannot be produced by *de novo* synthesis in mammals, but have to be obtained from the diet. Thus, the shikimate pathway is a particularly attractive target for the design of specific enzyme inhibitors. Compounds fulfilling this function would be selective herbicides or antibiotics.

Raphael *et al,*[33] published the first total synthesis of shikimic acid in 1960. Since then, many other different approaches to both racemic and optically active forms of shikimic acid have been reported.[34,35] In this section the more recent synthetic studies will be reviewed, covering 1988 to date.

1.2.1 Birch *et al.*

Birch *et al.* have prepared the optically active form of the key intermediate **26a**, used in the synthesis of Campbell and Sainsbury,[36] using iron tricarbonyl as a lateral control group. (-)-Methyl shikimate was prepared from either of the resolved iron tricarbonyl complexes **23** and **27** obtained from 1,4-dihydrobenzoic acid. These complexes have previously been used in an enantiospecific synthesis of gabaculine.[37]

Starting form the (+)-complex **23** (**scheme 1.18**), the cationic salt **24** was formed. This had previously been shown to react with nucleophiles solely at the 5-*exo* position.[38] Thus, reaction of **24** with aqueous sodium hydrogen carbonate



(a) $Ph_3C^+ PF_6^-$, CH_2Cl_2; (b) $NaHCO_3$, MeCN, H_2O; (c) TBDMSCl, (*i*-Pr)$_2$NEt, DMF; (d) Me_3NO, PhH; (e) OsO_4, Me_2CO; (f) *n*-Bu_4NF, THF; (g) CrO_3, Py, CH_2Cl_2; (h) $NaBH_4$, $ZnCl_2$, Et_2O; (i) TBDMSOTf, (*i*-Pr)$_2$NEt, DMF.

Scheme 1.18

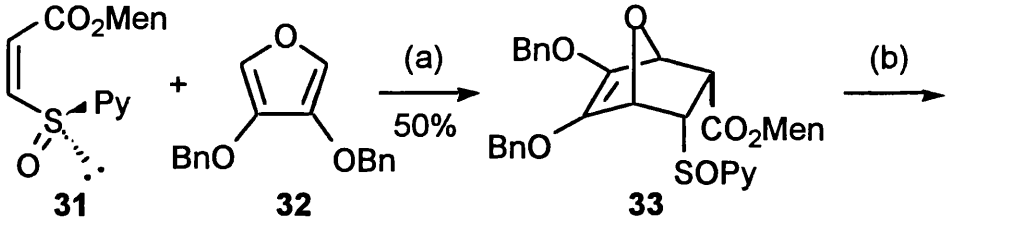
afforded the alcohol complex **25**. Protection as the TBDMS ether and decomplexation, yielded the (+) enantiomer of the Bath intermediate **26a**. This was converted into (-)-methyl shikimate via *cis*-hydroxylation and deprotection.

Starting from the (-)-complex **27**, a similar procedure led to the alcohol complex **29**, which has the wrong configuration at C-5. Inversion was achieved by Jones oxidation to the carbonyl compound, followed by a stereospecific reduction under reagent approach control, using sodium borohydride and zinc chloride,

afforded the alcohol complex **30**. Protection and decomplexation gave the required diene **26a**.

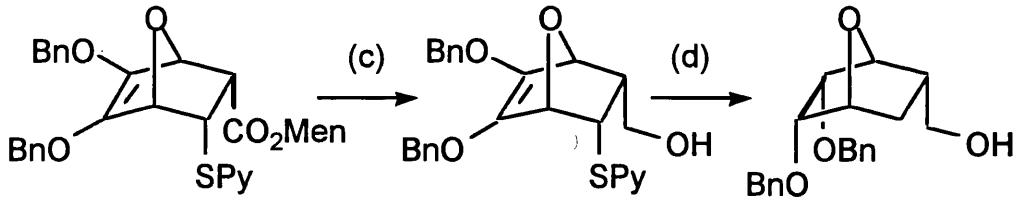
1.2.2 Koizumi *et al.*

Koizumi *et al.* have reported an enantioselective synthesis of methyl shikimate (**scheme 1.19**)[39]. An asymmetric Diels-Alder reaction between menthyl (S)-3-(2-pyridylsulfinyl)acrylate **31**[40a] and 3,4-dibenzyloxyfuran[40b] **32** yielded a mixture of *exo* and *endo* adducts, from which the major *endo* adduct **33** could be separated. Reduction of **33** to the sulfide **34**, followed by reduction of the ester gave the alcohol **35**. Treatment with Raney nickel resulted in desulfurisation and hydrogenation of the double bond to give the *endo-cis*-dibenzyloxy derivative **36**. Oxidation and esterification yielded the methyl ester **37**, which upon ring opening, debenzylation and acetylation afforded (-)-methyl triacetylshikimate **38**.

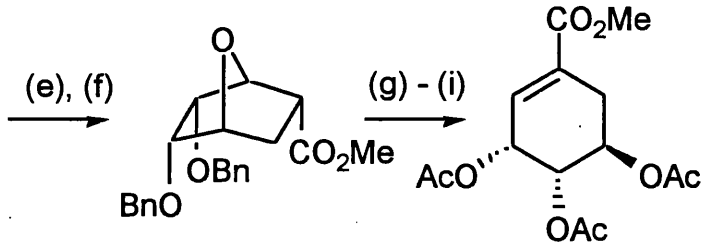


31 **32** **33**

Men = (-)-menthyl, Py = 2-pyridyl



34 **35** **36**



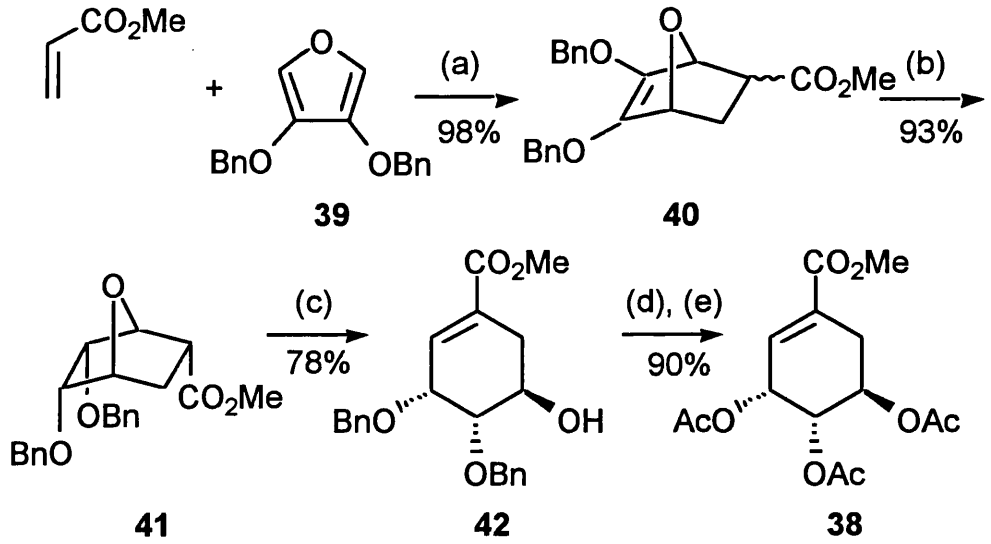
37 **38**

(a) Et_2AlCl; (b) PBr_3, DMF, 0^0C; (c) $LiAlH_4$, Et_2O; (d) Raney-Ni, EtOH; (e) CrO_3, Py, Me_2CO; (f) CH_2N_2, MeOH, Et_2O; (g) $LiN(TMS)_2$, THF, -78^0C; (h) TMSCl, NaI, MeCN; (i) Ac_2O, Py.

Scheme 1.19

1.2.3 Koreeda *et al.*

The use of 3,4-dibenzyloxyfuran **32** as a precursor to shikimic acid was also reported simultaneously by Koreeda *et al.*[41] in a synthesis of racemic methyl triacetylshikimate (**scheme 1.20**). The Diels-Alder reaction of **39** with methyl acrylate, catalysed by zinc iodide, yielded the adduct **40** as a mixture of *exo* and *endo* adducts (ratio 15:1). The *endo* adduct was subsequently hydrogenated to afford the required *endo-cis*-dibenzyloxy derivative **41**. Ring opening, debenzylation and subsequent purification of the resulting triol, as its triacetate, afforded methyl triacetylshikimate **38** in 60% overall yield from **39**.



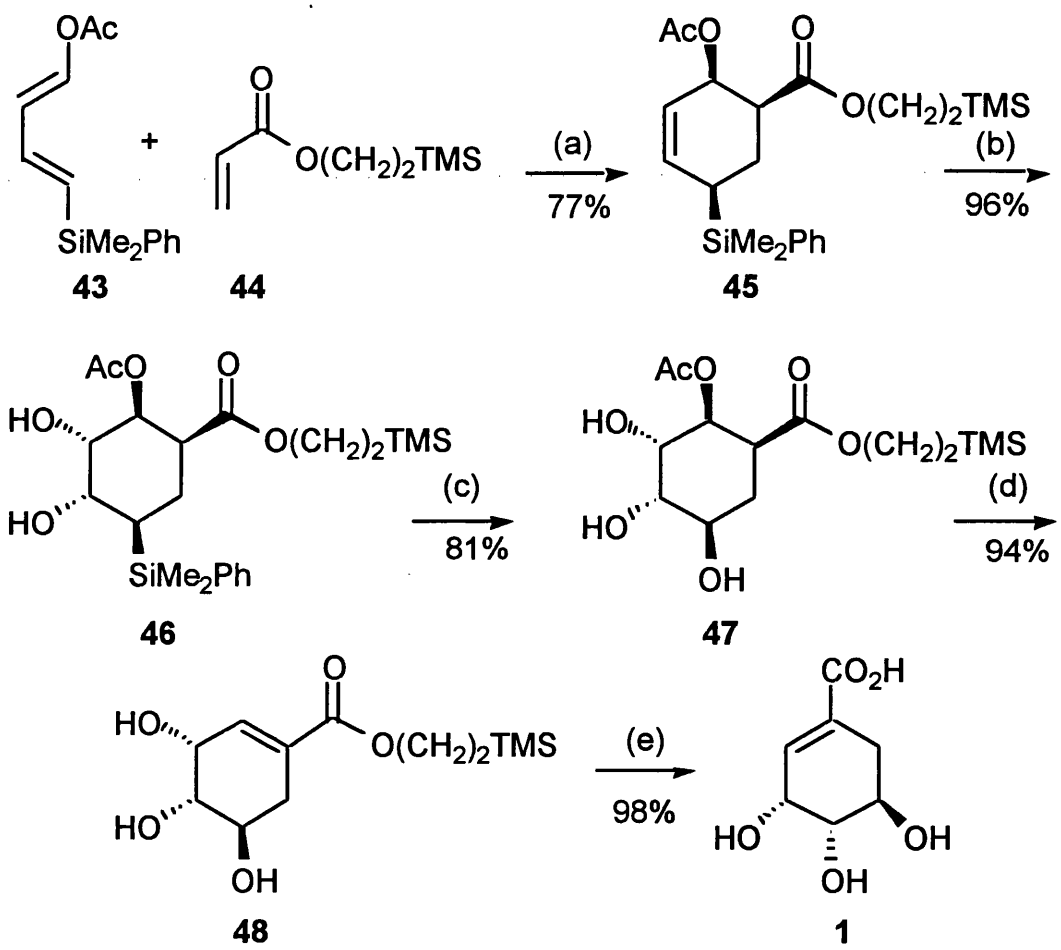
(a) ZnI_2; (b) H_2, PtO_2, EtOAc; (c) $LiN(TMS)_2$, THF, -78^{0}C;
(d) $BF_3.OEt_2$, EtSH, CH_2Cl_2, 0^{0}C; (e) Ac_2O, Py.

Scheme 1.20

1.2.4 Koreeda *et al.*

Koreeda has also recently published a total synthesis of racemic shikimic acid from (1*E*,3*E*)-4-acetoxy-1-dimethylphenylsilyl-1,3-butadiene **43**.[42] This is essentially an improved version of his earlier synthesis[43] and demonstrates the use of the diene **43** as a surrogate for (1*E*,3*E*)-1,4-diacetoxy-1,3-butadiene (**scheme 1.21**).

The Diels-Alder reaction of **43** with 2-(trimethylsilyl)ethyl acrylate **44** yielded the adduct **45** as the major product. *cis*-Hydroxylation afforded the diol **46**, which was subjected to Fleming's one-pot buffered oxidation procedure[44] to yield the triol **47**. Base mediated elimination produced 2-(trimethylsilyl)ethyl shikimate **48**, which was deprotected to produce shikimic acid in an overall yield of 55% from **43**.

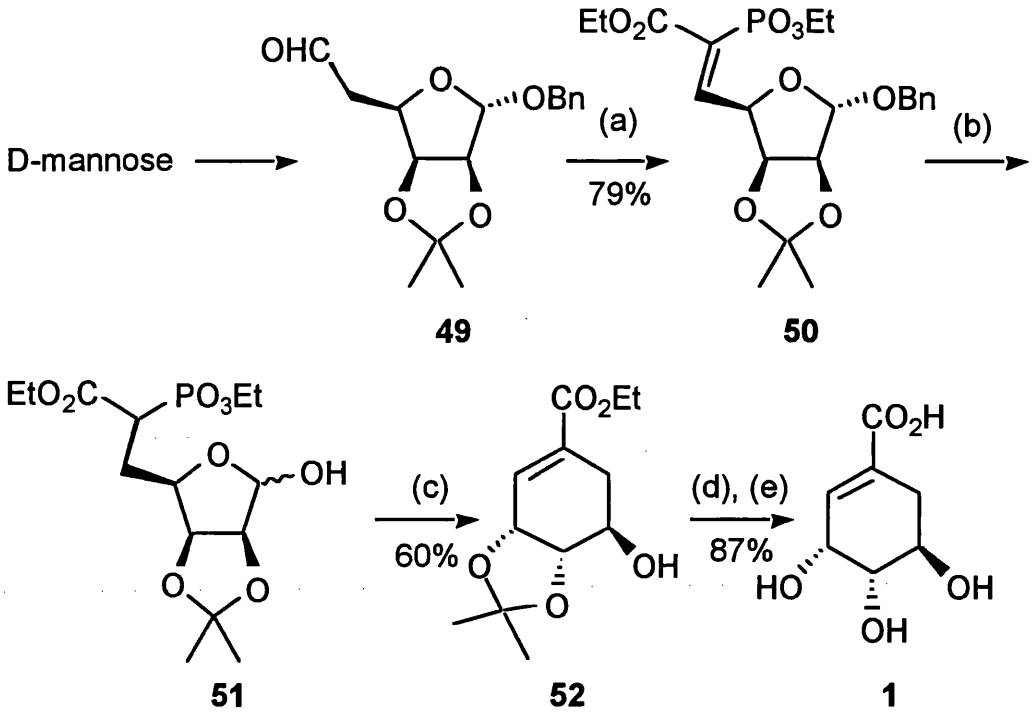


(a) hydroquinone monomethyl ester (cat.), xylene, reflux; (b) OsO_4, NMO, THF, H_2O; (c) KBr, AcOOH, AcOH, AcONa; (d) DBU, THF; (e) *n*-Bu_4NF, THF.

Scheme 1.21

1.2.5 Mirza *et al.*

An intramolecular olefination was employed in the recent synthesis by Mirza *et al.* (**scheme 1.22**).[45] *D*-Mannose was converted into the suitably protected



(a) $(EtO)_2P(O)CH_2CO_2Et$, *N*-methyl morpholine, $TiCl_4$, CCl_4, THF; (b) H_2, Pd-C, EtOH; (c) NaOEt, EtOH; (d) aq NaOH, EtOH; (e) Dowex 50W-X4 (H^+, H_2O).

Scheme 1.22

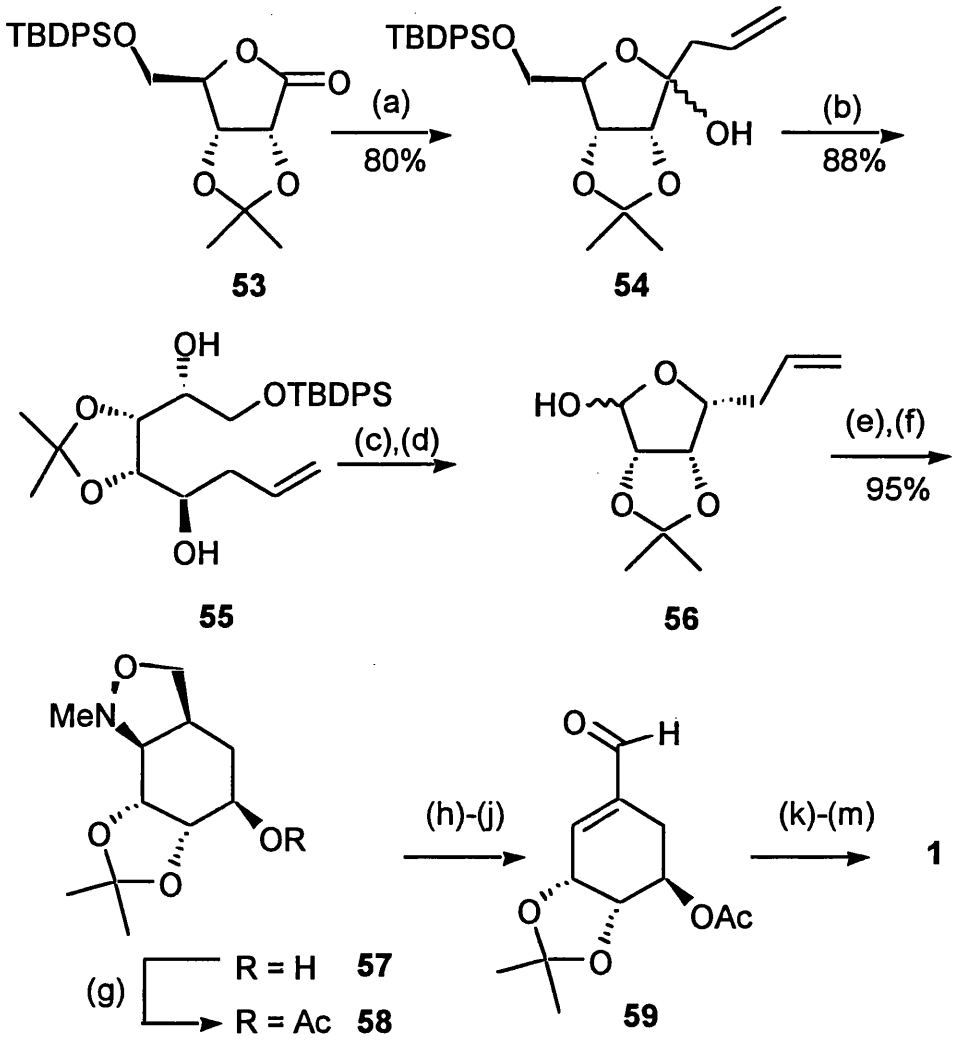
D-lyxose-5-aldehyde **49**, [46] which was condensed with triethylphosphonoacetic acid to afford **50**. Hydrogenation gave the hemiacetals **51**, which on treatment with base underwent an intramolecular olefination to yield ethyl 3,4

-isopropylidene shikimate **52**. Deprotection afforded (-)-shikimic acid in 27% overall yield from *D*-mannose.

1.2.6 Singh, Wightman *et al.*

Singh, Wightman *et al.* have recently published a synthesis of shikimic acid starting from *D*-ribose (**scheme 1.23**).[47] Compound **53** is formed from 2,3-*O*-isopropylidene-*D*-ribose by either sequential silylation and oxidation, or from *D*-ribonolactone.[48] **53** was treated with allylmagnesium chloride, at low temperatures,

to yield the lactol **54** as an anomeric mixture. This was then reduced with DIBAL to give a single diol **55**. Desilylation of **55**, followed by periodate cleavage, gave the hemiacetals **56**. Treatment with MeNHOH.HCl in pyridine, followed by heating of the crude nitrone in toluene, led to a single isoxazoline **57**, which was acetylated to give **58**. Hydrogenation of **58** over Pearlman's catalyst, quarternisation, and Swern oxidation gave aldehyde **59**. Oxidation with $NaClO_2$-H_2O_2, deactylation and acid hydrolysis gave (-)-shikimic acid **1**.

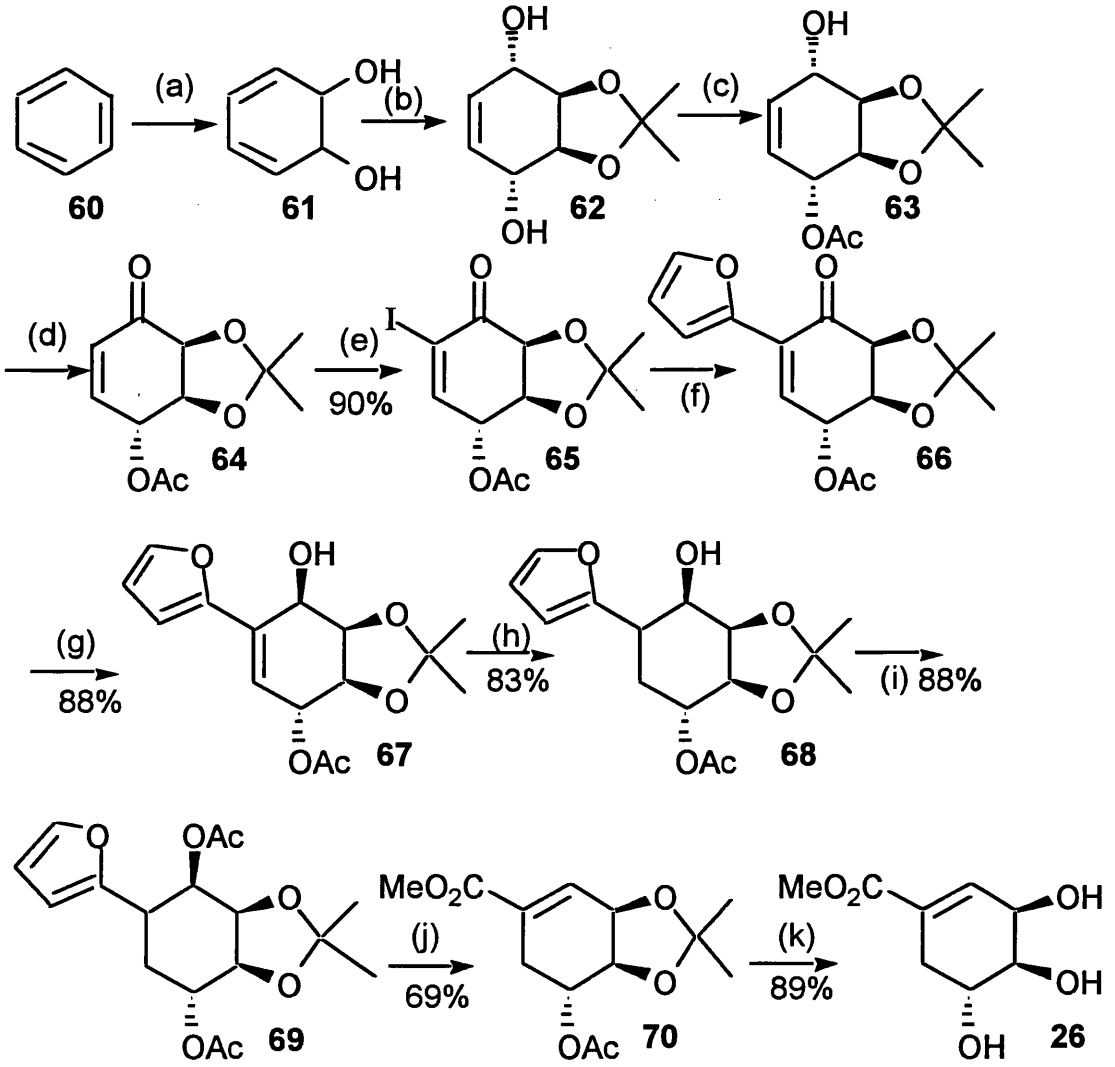


(a) allyl MgCl, THF, -78 °C, 3 hr. (b) DIBAL, PhMe, -78 °C, 3 hr. (c)TBAF, THF (d) $NaIO_4$, H_2O, r.t. 2 hr. (e) MeNHOH.HCl, C_5H_5N, r.t. 20 hr. (f) PhMe, reflux, 18 hr. (g)Ac_2O, DMAP, C_5H_5N. (h) $Pd(OH_2)$/C, H_2 ($_2$ atm), MeOH. (i) MeI, K_2CO_3, THF, r.t. 30 hr. (j) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, 55 min, then ET_3N, -78 °C to r.t. (k) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t. 1 hr. (l) K_2CO_3, MeOH-H_2O, r.t. (m) TFA-H_2O, r.t.

Scheme 1.23

1.2.7 Johnson *et al.*

Johnson et al.[49] has recently synthesised (+) and (-)-methyl shikimate from benzene (**scheme 1.24**). Benzene **60** was oxidised by mutants of the micro-organism *Pseudomonas putida* to the diol **61**[50], this was then converted into *meso*-diol **62** and then was asymmetrised to mono-acetate **63** utilizing *Pseudomonas cepacia* lipase in isopropenyl acetate.[51] The mono-acetate was then oxidised using PCC[52] to generate

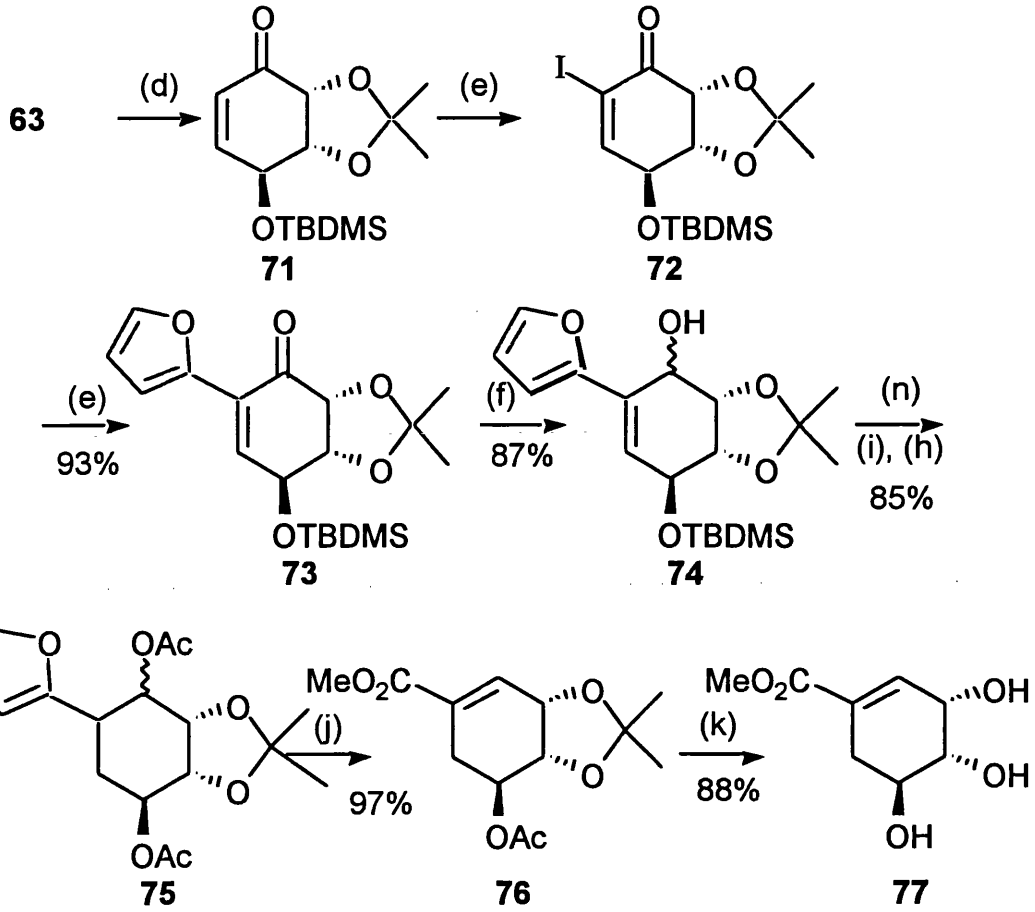


(a) *Pseudomonas putida*. (b) ref 49b and 49c. (c) *Pseudomonas cepacia* lipase, isopropenyl acetate. (d) Pyridinium chlorochromate, CH_2Cl_2, molecular sieves. (e) I_2-pyridine CCl_4. (f) 2-tributylstannylfuran, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, *N*-methylpyrrolidone (g) $CeCl_3$, $NaBH_4$, MeOH, -78°C. (h) H_2, Pd on C, EtOH. (i) Ac_2O, 4-dimethyl-aminopyridine, Et_3N, CH_2Cl_2. (j) 1- $RuO_2.H_2O$, $NaIO_4$, CCl_4, H_2O, CH_3CN. 2- CH_2N_2, Et_2O. 3- DBU, CH_2Cl_2, 20°C, 12 hr. (k) TsOH, MeOH, reflux.

Scheme 1.24

enone **64**. Treatment with iodine in carbon tetrachloride-pyridine furnished the α-iodoenone **65** in 80% yield. Furan **66** was isolated in quantitative yield when the α-iodoenone **65** and 2-tributylstannylfuran were coupled under Stille conditions.[53] The enone **66** was reduced under Luche conditions[54] to furnish a mixture of readily separable epimeric allylic alcohols **67** (ratio 6:1). Hydrogenation afforded **68**, whilst acylation of the alcohol **68** produced the diacetate **69**. Oxidation of the furan group of **69** with ruthenium tetroxide,[55] followed by esterification of the crude acid with diazomethane and elimination of the acetate furnished the α,β–unsaturated acid **70**. Deprotection of the three hydroxyl groups was accomplished by treatment of **70** with toluene-*p*-sulfonic acid in boiling methanol to afford (-)-methyl shikimate **26**.

The unnatural (+)-methyl shikimate **77** was also prepared from **63** (**scheme 1.25**). The hydroxyl group of **63** was first protected as a TBDMS ether, elimination of the acetate and subsequent PCC oxidation of the resulting alcohol afforded **71**. The α-iodoenone **72** was prepared by treating **71** with iodine in carbon tetrachloride-pyridine. Furan **73** was prepared from **72** as before. Luche reduction of this compound afforded a 1:1 mixture of the epimeric alcohols **74**. Deprotection of the *tert*-butyldimethylsilyl group, diacetylation and hydrogenation afforded **75**. Oxidation, esterification, and elimination was carried out as for **69** (**scheme 1.24**) to afford the α,β–unsaturated ester **76**. Deprotection of the acetonide and the acetate in acidic methanol yielded (+)-methyl shikimate **77**.



(l) TBDMSCl, imidazole, DMF; (m) K_2CO_3, MeOH;(n) tetrabutylammonium fluoride, THF, 25°C, 24 hr

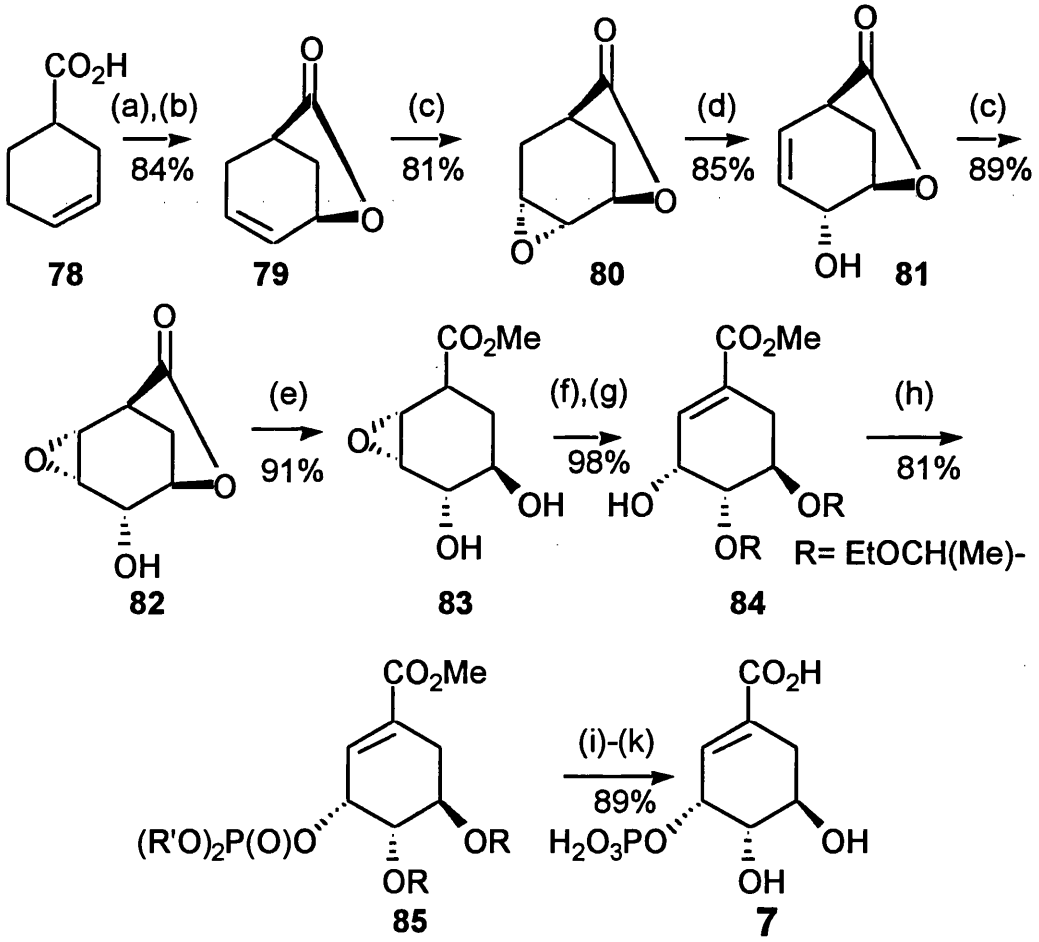
Scheme 1.25

1.3 Synthesis of Later Intermediates in the Shikimate Pathway

1.3.1 Shikimic acid 3-phosphate

The first synthesis of shikimic acid 3-phosphate was reported by Bartlett *et al.*,[56] (**Scheme 1.27**). Cyclohex-3-ene-1-carboxylic acid **78** underwent iodolactonisation, followed by DBU induced elimination to give the lactone **79**. This was converted to the epoxide **80**, which was opened with trimethylsilyl bromide, the resulting trimethylsilyl bromohydrin was eliminated with DBU and after aqueous workup gave the alcohol **81**. Epoxidation gave the epoxy alcohol **82** which upon

methanolysis gave (±)-methyl shikimate **26**. Methanolysis of **82** at a lower temperature gave the epoxy diol **83**. Protection and opening of the epoxide afforded protected shikimate derivative **84** in which the 3-OH is free. Phosphorylation [57] yielded the phosphate triester **85** which was deprotected with DBU. Hydrolysis and cleavage of the acetal protecting groups, followed by ion exchange chromatography yielded (±)-3-phosphoshikimic acid 7.



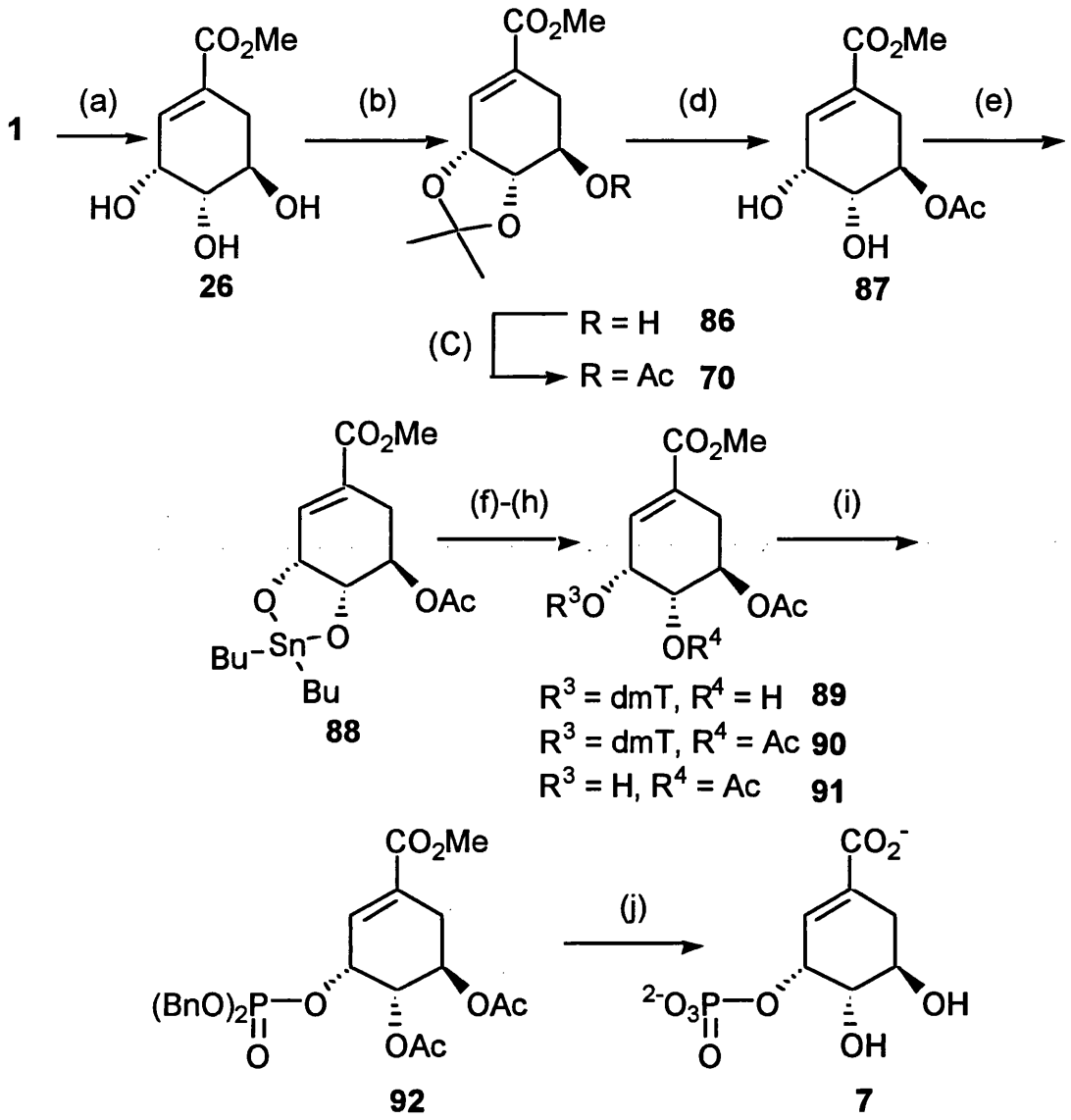
(a) I_2, KI, $NaHCO_3$, H_2O; (b) DBU, THF, reflux; (c) 3,5-dinitro-perbenzoic acid, CH_2Cl_2; (d) TMSBr, Ph_3P, MeCN then DBU, reflux; (e) K_2CO_3, MeOH; (f) ethyl vinyl ether, PPTS, THF; (g) K_2CO_3, MeOH; (h) bis(*p*-nitrophenylethyl) phosphoro chloriodate, Py, DMAP, CH_2Cl_2; (i) DBU, $CHCl_3$; (j) aq. NaOH; (k) Dowex 50W-X8 (H^+), H_2O.

Scheme 1.26

(±)-3-Phosphoshikimic acid 7 has also been synthesised by Tisnès *et al.*[58] (**Scheme 1.27**). Methyl shikimate **26** was protected as the acetonide **86**. This was converted in two steps by acylation and cleavage of the acetal protection to give the 3,4-diol **87**. This was then reacted with dibutyltin oxide to give O-stannylene acetal **88**. By reacting this with dimethoxytrityl chloride for less than one hour gave **89**. For longer periods the dimethoxytrityl group partially migrates from the 3 to the 4 position. After acetylation of the 4-hydroxyl group (**90**) the dimethoxytrityl group was removed using aqueous acetic acid and tetrahydrofuran to give the diacetate **91**. This was phosphorylated to give **92** . After debenzylation with bromotrimethylsilane and hydrolysis, (-)-shikimate 3-phosphate **7** was afforded as its sodium salt in an overall yield of 32% from shikimic acid.

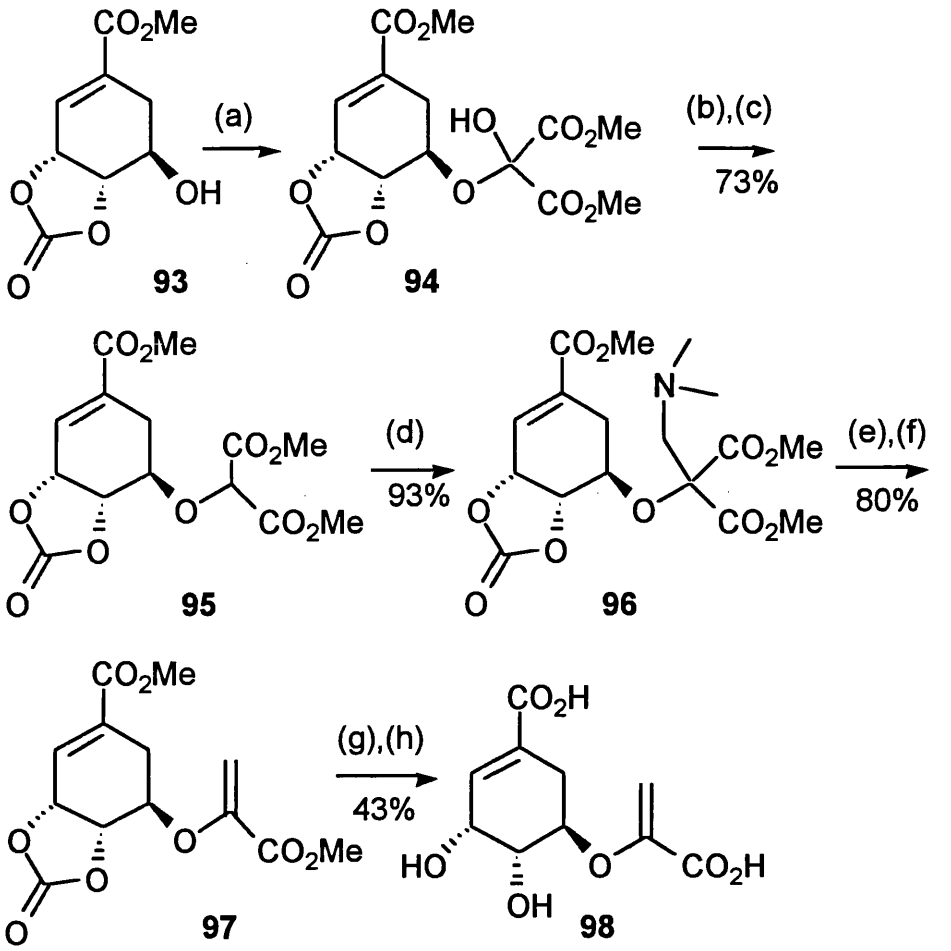
1.3.2 5-Enolpyruvylshikimate-3-phosphate (5-EPS-3-P)

The construction of the enolpyruvyl functionality of 5-EPS-3-P and chorismic acid, was first demonstrated by Berchtold *et al.*[59] in a synthesis of 5-enolpyruvylshikimate 98 (**scheme 1.28**). The carbonate derivative of (-)-methyl shikimate **93** was reacted with dimethyloxomalonate to afford the hemiketal 94. Treatment with thionyl chloride followed by reduction, yielded **95**, which was converted to the Mannich base **96**. Quarternisation gave the quaternary ammonium iodide, which upon heating underwent decarboxylation and elimination to afford **97**. Hydrolysis of **97** gave 5-enolpyruvylshikimic acid **98** or 'compound Z_1'.[60] Compound Z_1 has been observed as a secondary metabolite from hydrolytic cleavage of the phosphate ester group of 5-EPS-3-P, but has no known biological function.



(a) Amberlite resin, MeOH; (b) 2,2-dimethoxypropane, *p*-TSA; (c) DMAP, acetic anhydride, CH_3Cl; (d) AcOH-THF-H_2O (39:11:6), 70^0C, 6 h; (e) Bu_2SnO, PhH, reflux; (f) dimethoxytrityl chloride, DMF; (g) DMAP, acetic anhydride, CH_2Cl_2; (h) AcOH, H_2O; (i) tetrazole, dibenzyl *N,N*-diethylphosphoramidite, CH_2Cl_2, then MCPBA, -40^{0}C; (j) TMSBr.

Scheme 1.27

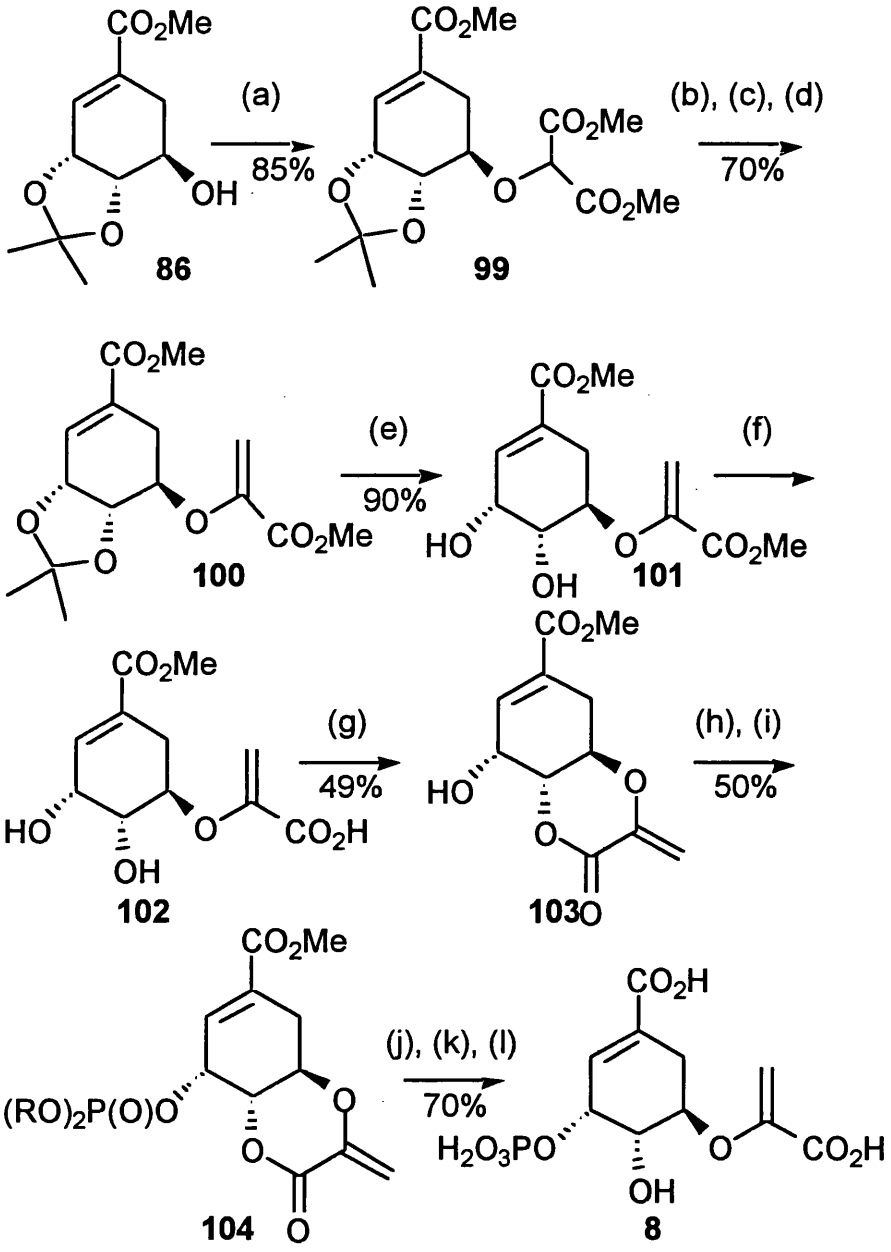


(a) $(MeO_2C)_2CO$, PhH, reflux; (b) $SOCl_2$, Py, THF, 0^0C; (c) Zn, 90% aq. AcOH, 0^0C; (d) $CH_2{=}NMe_2^+$ I^-, Et_3N, CH_2Cl_2; (e) MeI, CH_2Cl_2, reflux; (f) DMSO, 80^0C; (g) aq. NaOH; (h) Amberlite IR 120 (+), H_2O.

Scheme 1.28

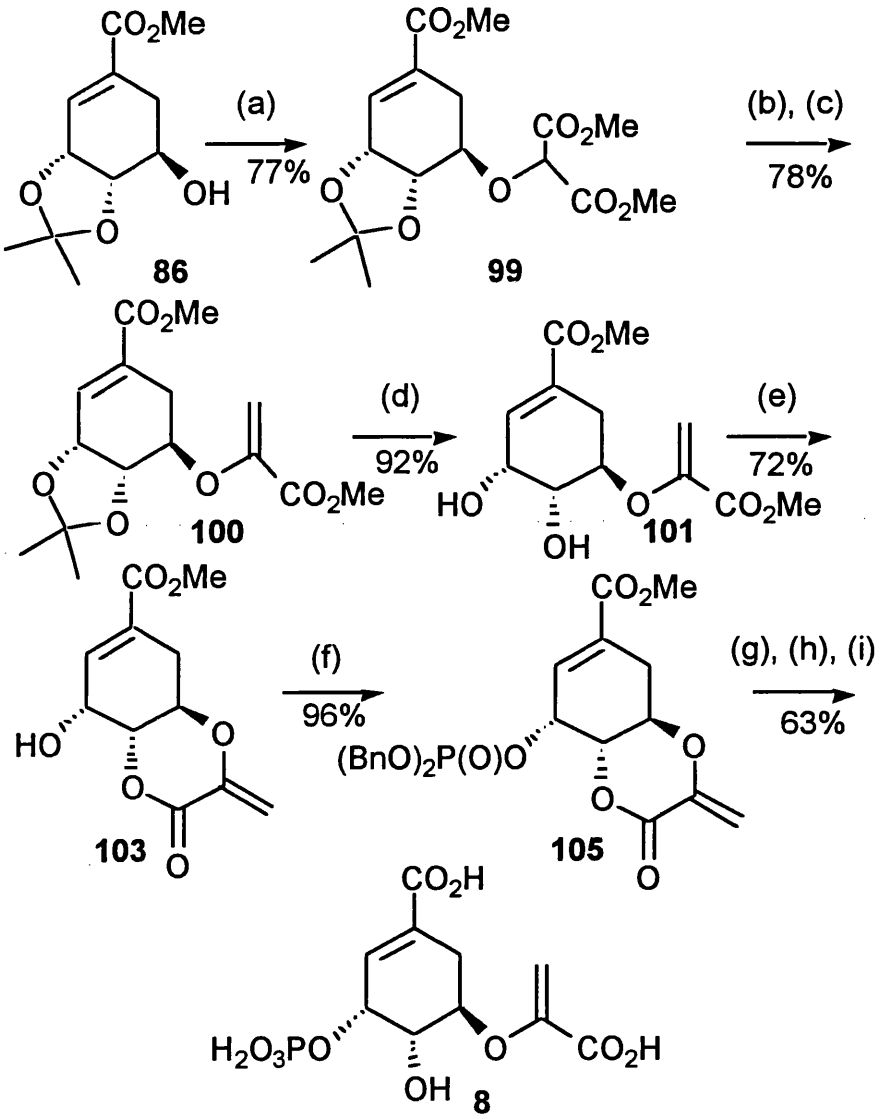
The first synthesis of 5-EPS-3-P was reported by Ganem *et al.*[61] (**scheme 1.29**). The acetonide of (-)-methyl shikimate **86** was converted to the alkoxymalonate **99** by the $Rh_2(OAc)_4$ catalysed insertion of dimethyl diazomalonate. Reaction with Eschenmoser's reagent, quarternisation and decarboxylation/elimination, in a similar sequence to that used by Berchtold[59], afforded the enolpyruvate **100**. Deprotection

afforded the diol **101**, which was selectively hydrolysed to yield the monoacid **102**. Cyclisation of **102** gave the bicyclic lactone



(a) $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, PhH, reflux; (b) $CH_2{=}NMe_2^+ I^-$, Et_3N, CH_2Cl_2 (c) MeI, CH_2Cl_2, (d) DMSO, 95^0C; (e) 80% aq. AcOH, 70^0C; (f) aq. NaOH (1.1 equiv.), THF; (g) DCC, DMAP, THF; (h) PCl_3, Py, THF then p-$NO_2C_6H_4(CH_2)_2OH$; (i) I_2, H_2O, -78 to 0^0C; (j) DBU, Py; (k) aq. NaOH; (l) Amberlite IR 120 (+).

Scheme 1.29



(a) $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, PhH, 85^0C; (b) $CH_2=NMe_2^+$ I$^-$, Et_3N, CH_2Cl_2; (c) MeI, MeCN, reflux; (d) 65% aq. AcOH, THF, 70^0C; (e) K_2CO_3, MeCN;(f) LDA, $[(BnO)_2P(O)]_2O$, THF, -78^0C; (g) TMSBr, Py, CH_2Cl_2, 0^0C;(h) aq. NaOH then ion-exchange resin.

Scheme 1.30

103. Phosphorylation of **103** *via* the bis(*p*-nitrophenylethyl)phosphite, gave the phosphate **104**. Deprotection afforded 5-EPS-3-P 8 as the sodium salt after ion-exchange chromatography.

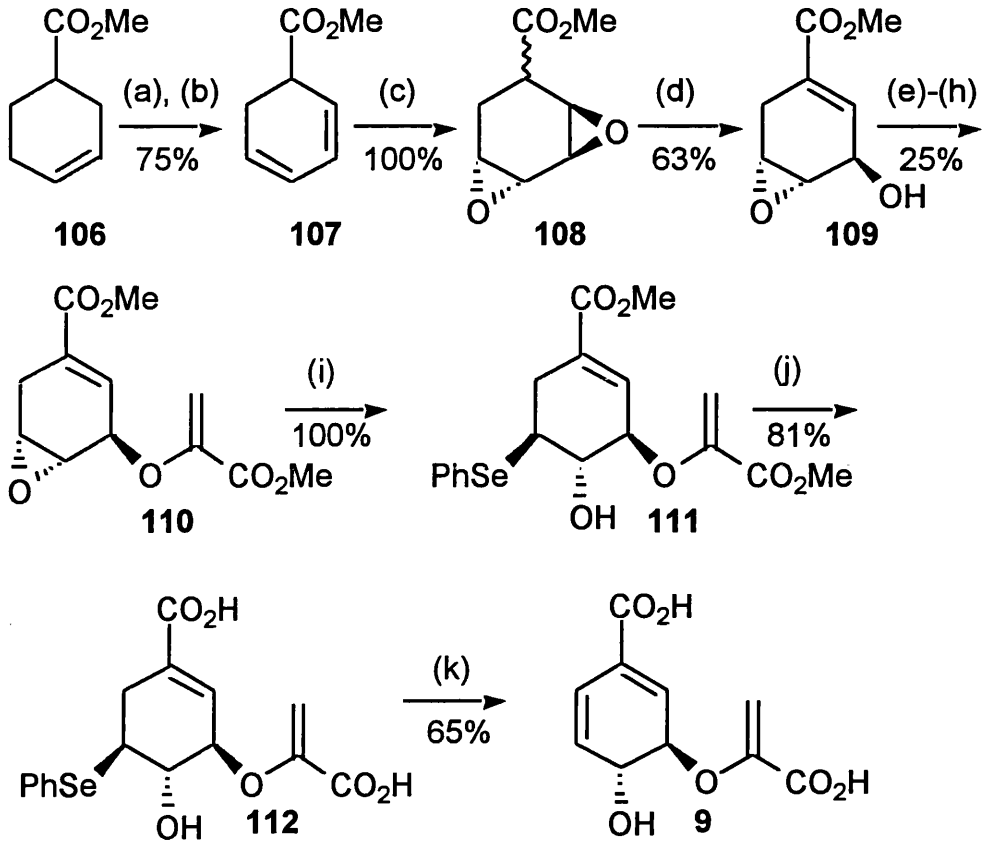
Bartlett *et al.*[62] published a similar synthesis (**scheme 1.30**), in which the early steps are virtually identical. However, the lactone **103** was produced by direct

cyclisation of the diol **101** with potassium carbonate. Phosphorylation was achieved using tetrabenzylpyrophosphate to afford the phosphate triester **105**. Deprotection of the benzyl esters with trimethylsilyl bromide followed by alkaline hydrolysis gave 5-EPS-3-P **8**.

1.3.3 Chorismic Acid

Berchtold *et al.*[59, 63] reported the first total synthesis of (±)-chorismic acid in 1982. An improved synthesis was later published by the same group (**scheme 1.31**).[64]

Bis allylic bromination of **106** gave a mixture of dibromides, that were debrominated to afford the diene **107**. Epoxidation of **107** yielded **108**, which was isomerised to **109** on treatment with DBU. The enolpyruvyl side chain was constructed using either Berchtold's[59,63] or Ganem's[61] procedure to afford **110**. The epoxide was then opened with $PhSe^-$ to give **111**, which was hydrolysed to the diacid **112**. Selenoxide elimination from **112**, in the presence of 3,5-dimethoxyaniline as a PhSeOH scavenger, afforded chorismic acid **9**.

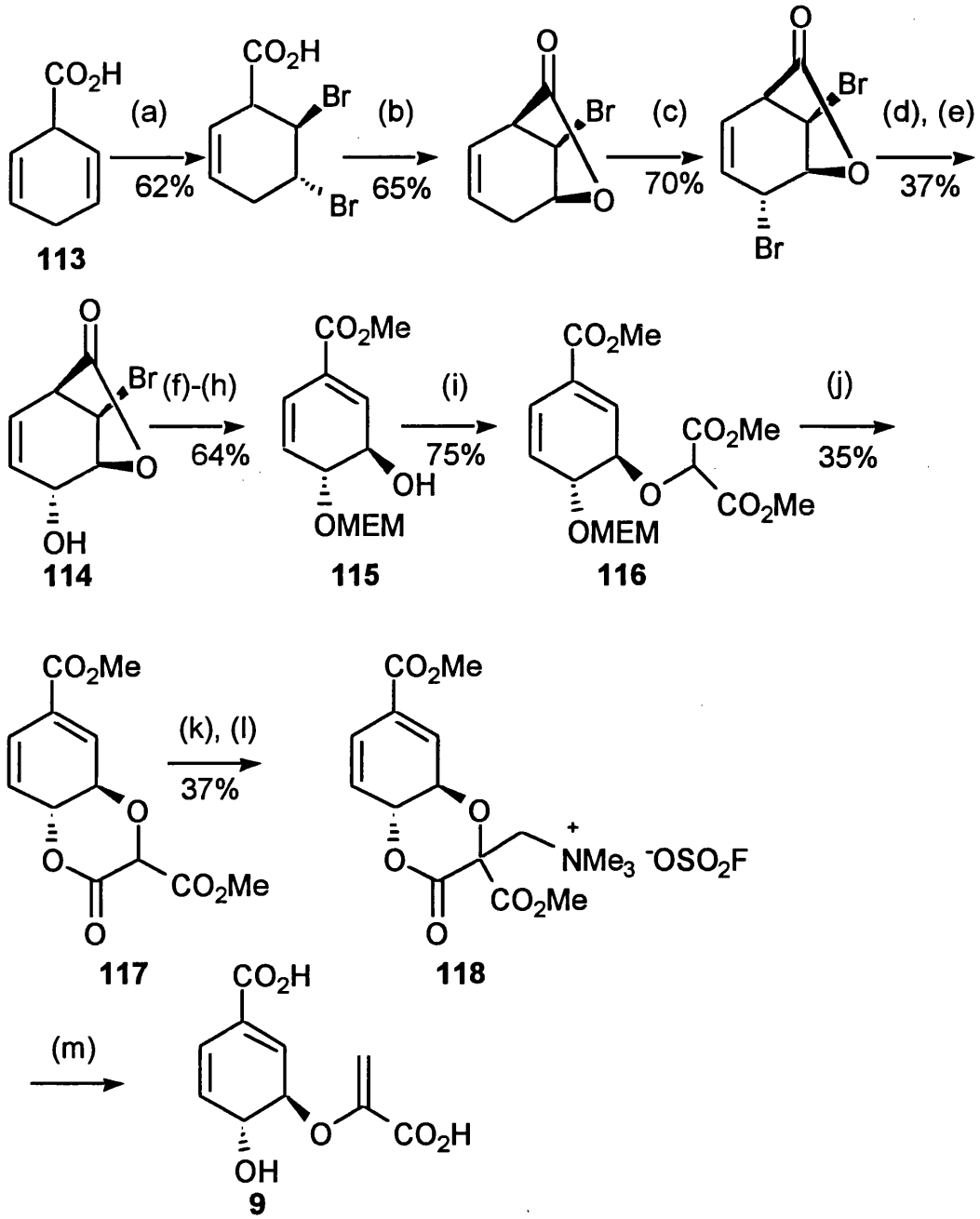


(a) NBA, AIBN, CCl_4, reflux; (b) Bu_3SnH, AIBN, PhH, reflux; (c) MCPBA, CH_2Cl_2; (d) DBU, CH_2Cl_2; (e) $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, PhH, 65^0C; (f) $CH_2{=}NMe_2{}^+I^-$, Et_3N, CH_2Cl_2; (g) MeI, CH_2Cl_2; (h) DMSO, 80^0C; (i) $(PhSe)_2$, $NaBH_4$, MeOH; (j) aq. NaOH, THF, 0^0C; (k) H_2O_2, DMA, Me_2CO, -35^0C to 20^0C.

Scheme 1.31

A total synthesis of (±)-chorismic acid was also published in 1982 by Ganem *et al.*[65] The bicyclic allylic alcohol **114** was first prepared from 1,4-dihydrobenzoic acid **113 (scheme 1.32)**.[66] Protection of the hydroxyl group as its MEM ether, saponification and esterification yielded **115**. The $Rh_2(OAc)_4$ catalysed insertion of dimethyl diazomalonate afforded **116**, which was cyclised to give the bicyclic lactone **117**. Alkylation with Potier's salt followed by quarternisation yielded **118**. Hydrolysis, decarboxylation and β-elimination in aqueous sodium hydroxide afforded chorismic acid **9**.

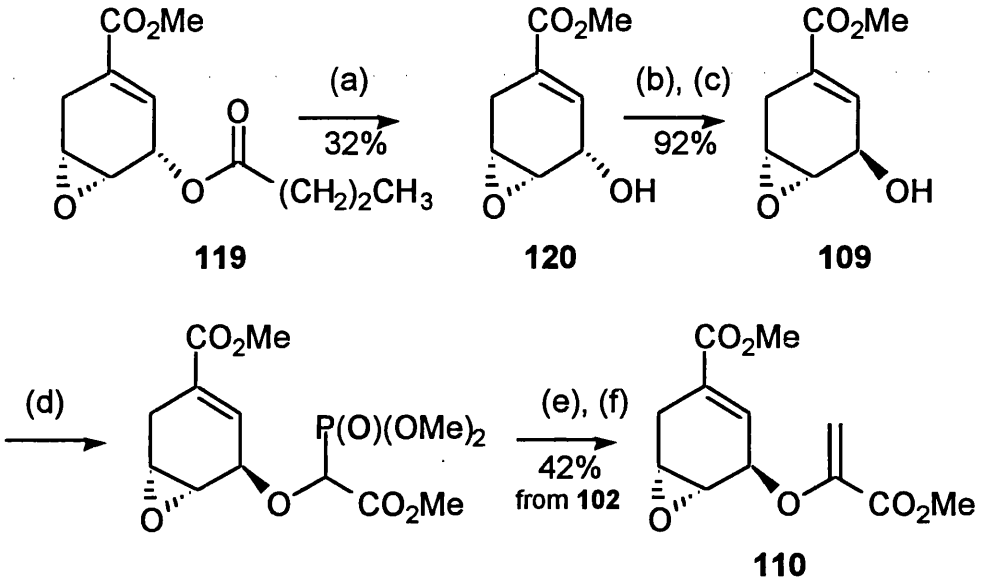
The enantiospecific synthesis of chorismic acid has been accomplished by both Berchtold and Ganem. Berchtold has described



(a) Br_2, CH_2Cl_2; (b) aq. $NaHCO_3$; (c) NBS, $(PhCO_2)_2$, CCl_4, reflux; (d) NaOAc, HMPA; (e) 10 % aq. H_2SO_4, THF, reflux; (f) MEM-$Et_3N^+Cl^-$, MeCN, reflux; (g) aq. KOH, THF; (h) MeI, HMPA; (i) $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$, PhH, 65^0C; (j) *p*-TSA, PhH, H_2O; (k) $CH_2=NMe^+CF_3CO_2^-$; (l) FSO_2OMe, $CDCl_3$; (m) aq. NaOH, THF.

Scheme 1.32

the synthesis of an enantiomerically pure intermediate for his earliest synthesis of chorismic acid[59,63] from quinic acid.[67] The key intermediate **109** used in his second synthesis (**scheme 1.31**) was also prepared in chiral form.[68] An enantioselective enzymatic hydrolysis of the *n*-butyrate ester **119**, followed by inversion of the configuration of the carbinol carbon of **120**, afforded **109** (**scheme 1.32**). The enolpyruvyl side chain was attached in a different manner, *via* coupling with methyl diazophosphonoacetate and reaction with formaldehyde to yield **110**. Transformation of **110** into chorismic acid was accomplished as described earlier.[63]

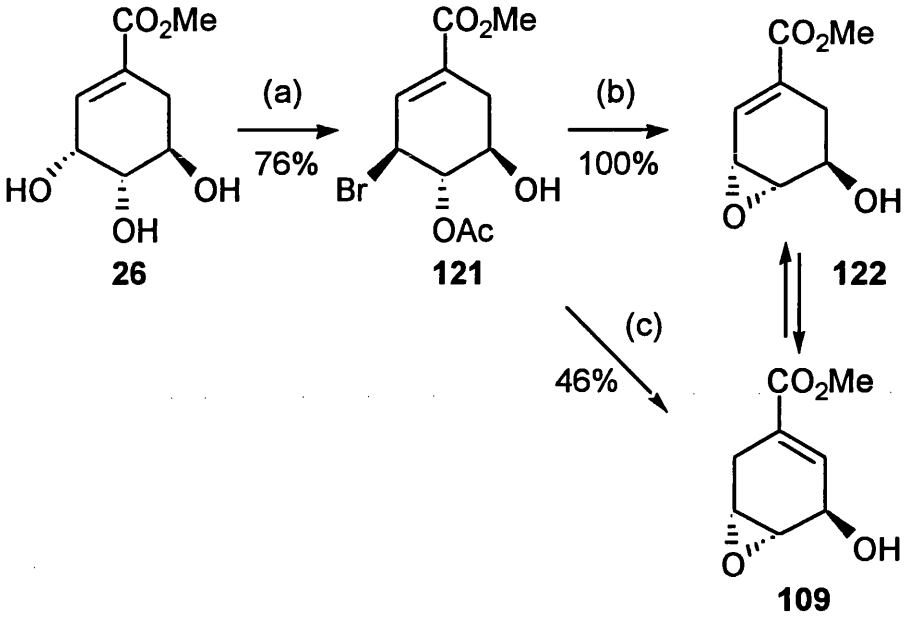


(a) cholesterol esterase, H_2O, pH 7.8, 0 to 5^{0}C; (b) *i*-$PrO_2CN{=}NCO_2$-*i*-Pr, Ph_3P, AcOH, THF; (c) NaOMe, MeOH; (d) $MeO_2CC(N_2)P(O)(OMe)_2$, Rh_2(*n*-$C_7H_{15}CO_2)_4$, PhH, reflux; (e) $LiN(TMS)_2$, THF, -78^{0}C; (f) H_2CO, -78^{0}C

Scheme 1.33

Ganem *et al.* have developed an alternative route to Berchtold's epoxide 109.[69] The reaction of (-)-methyl shikimate **26** with 2-acetoxyisobutyryl bromide[70] yielded *trans*-bromoacetate **121** (**scheme 1.34**). Transesterification with sodium methoxide in methanol led to the epoxide **122**. This epoxide, also known as methyl 3,4-anhydroshikimate, had previously been reported in the literature,[71] although the specific rotation was different from that observed by Ganem.[69] This discrepancy was attributed to a Payne rearrangement to **109**, previously undetected by the earlier

workers.[72] Prolonged exposure of **122** to sodium methoxide produced a 1:3 mixture of **122:109**. The conversion of bromoacetate **121** to the epoxide **109** was possible, thus leading to a simple two step synthesis from (-)-methyl shikimate.



(a) α-acetoxyisobutyryl bromide, MeCN, 0^0C; (b) NaOMe, MeOH, 0^0C, 30 min; (c) NaOMe, MeOH, 0^0C, 30 min, then 50^0C, 35 min.

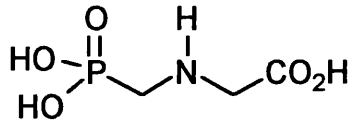
Scheme 1.34

1.4 Inhibition of Shikimate Pathway Enzymes

The shikimate pathway only occurs in plants and micro-organisms. The three aromatic amino acids produced by the pathway cannot be produced by *de novo* synthesis in animals, and have to be obtained from the diet. This makes the shikimate pathway a good target for enzyme inhibition, and any compounds fulfilling this function would be potential herbicides or antibiotics of low environmental impact.

Inhibitors are divided into two main classes, reversible and irreversible.[73] Reversible inhibitors undergo rapid equilibrium binding with the enzyme and are further classified as competitive, uncompetitive or non-competitive, depending on whether they bind to the free enzyme, enzyme-substrate complex or both, respectively. Irreversible inhibitors react covalently with an enzyme preventing substrate binding or catalysis.

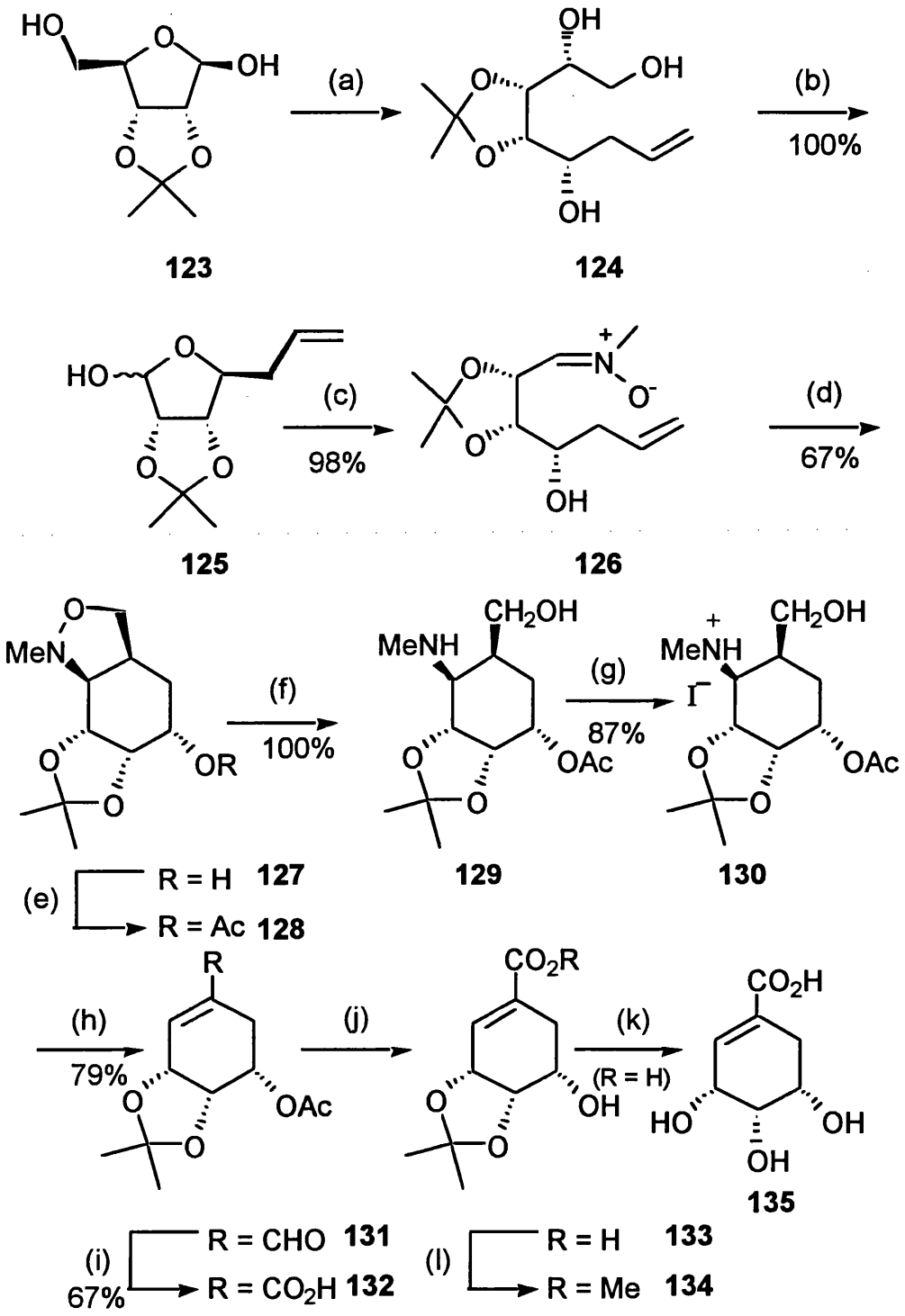
5-Enolpyruvylshikimate-3-phosphate synthase, which catalyses the conversion of shikimate 3-phosphate to 5-enolpyruvylshikimate-3-phosphate, is the most important enzyme in the shikimate pathway as an inhibitor target. Glyphosphate 122 (*N*-[phosphonomethyl]glycine),[74] the active ingredient of the broad spectrum herbicide Roundup®, effectively inhibits this enzyme.



122

1.4.1 Synthesis of Analogues of Shikimic Acid and Shikimate -3-Phosphate

Singh, Wightman *et al.* have described a synthesis of (-)-5-*epi*-shikimic acid **(scheme 1.35)**[47], which follows a similar route to their synthesis of (-)-shikimic acid **(scheme 1.23)**. 2,3-*O*-Isopropylidene-*D*-ribose **123** was converted into the *D-allo*-triol **124** by treatment with diallyl zinc.[75] Periodate cleavage of **124** gave **125** in quantitative yield, and on treatment with MeNHOH.HCl in pyridine, afforded nitrone **126**. Thermolysis of **126** yielded the cycloadduct **127**, which was acylated to afford **128**. Hydrogenation over Pearlman's catalyst gave the aminoalcohol **129**, and this could be converted to the quaternary salt **130** by treatment with MeI-K_2CO_3 in THF. When **130** underwent Swern oxidiation, β-elimination occurred spontaneously to



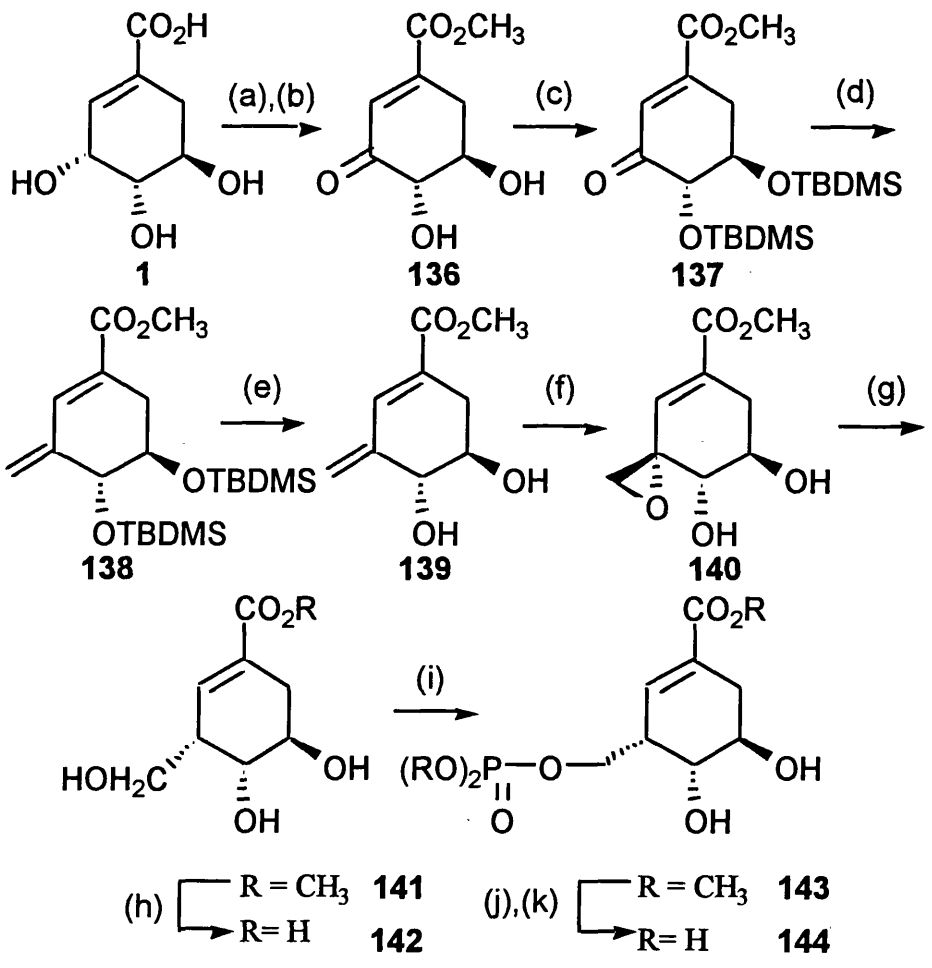
(a) diallylzinc, Et_2O, 0°C. (b) $NaIO_4$, H_2O, r.t. 2 hr. (c) MeNHOH.HCl, C_5H_5N, r.t. 17 hr. (d) PhMe, reflux, 17 hr. (e)Ac_2O, DMAP, C_5H_5N. (f) $Pd(OH_2)/C$, H_2, MeOH. (g) MeI, K_2CO_3, THF, r.t. 30 hr. (h) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, 50 min, then ET_3N, -78 °C to r.t. (i) $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN, r.t. 1 hr. (j) K_2CO_3, MeOH-H_2O, r.t. (k) TFA-H_2O, r.t. 10 hr. (l) CH_2N_2, Et_2O

Scheme1.35

afford enal **131**. This was readily oxidised to acid **132** using $NaClO_2$ and H_2O_2 under buffered conditions.[76] Deacetylation to give **133**, followed by acidic hydrolysis gave (-)-5-*epi*-shikimic acid **135**.

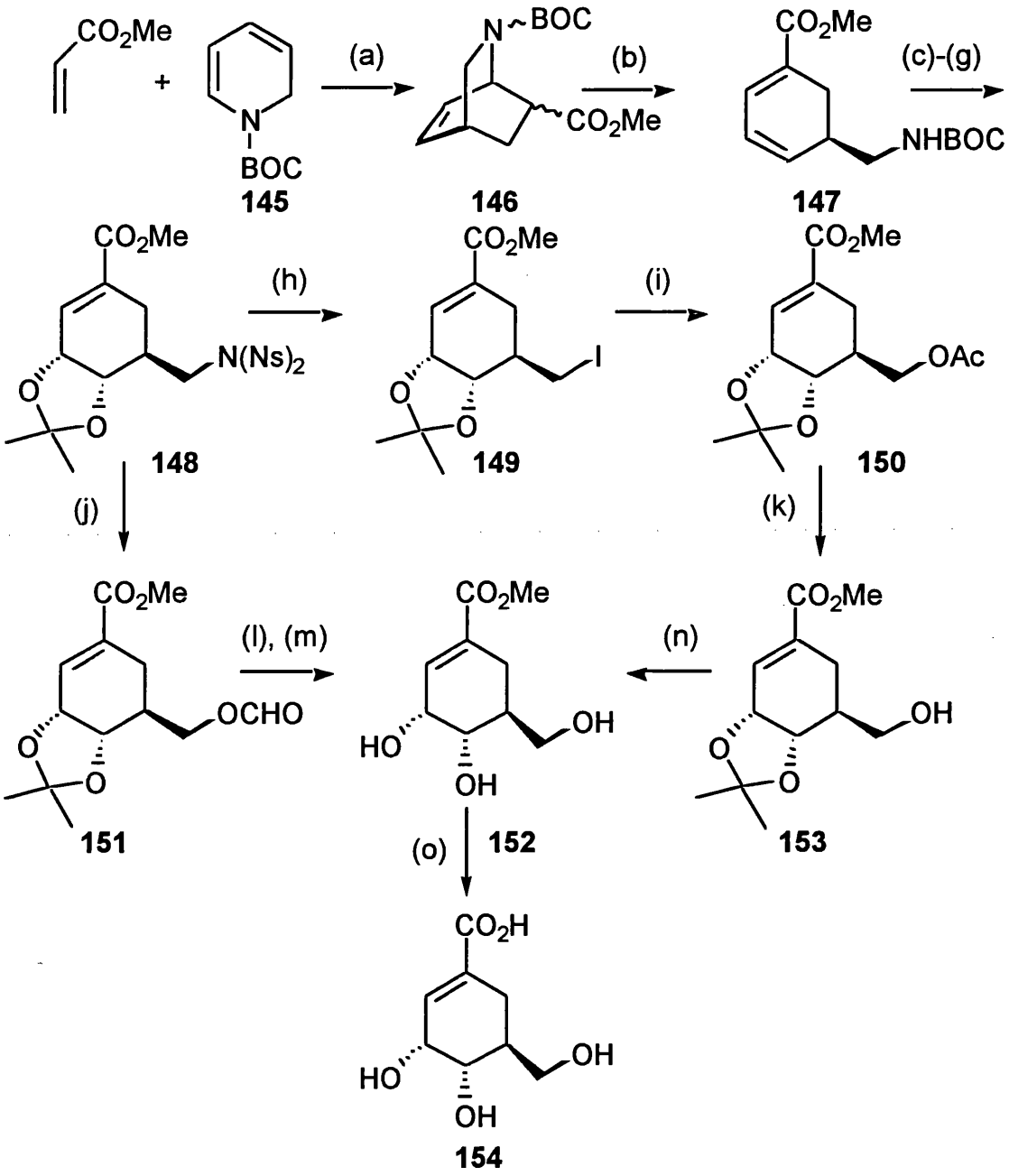
Ganem has synthesised both (-)-3-homoshikimic acid and (-)-3-homoshikimate-3-phosphate[77] (**Scheme 1.36**). 3-Dehydroshikimic acid which can be produced from shikimic acid (**1**) by either fermentation or by oxidation[78], was esterified to afford ester **136**. After silyl protection of the diol, TBDMSCl imidazole to yield **137**, methylenation afforded the diene **138**. Deprotection using tetrabutylammonium fluoride afforded enediol **139**. m-Chloroperoxybenzoic acid epoxidation selectively afforded **140**, which was reduced using sodium cyanoborohydride to give methyl 3-homoshikimate**141**.[79] This was hydrolysed to give 3-homoshikimic acid **142** which was phosphorylated using dimethylchlorophosphate to give triester **143**. Deprotection, hydrolysis and anion exchange chromatography gave 3-homoshikimate-3-phosphate **144**.

Campbell, Sainsbury *et al.* have published a synthesis of (±)-homoshikimic acid (**scheme 1.37**)[80] in which the 1,2-dihydropyridine **145** was reacted with methyl acrylate to yield 2-azabicyclo[2.2.2]oct-5-ene **146**. **146** was then ring opened with lithium hexamethyldisilazide to produce the diene **147**. Deprotection of the BOC protection group with TFA gave the amino ester, which was then converted into the disulphonimide. This was then treated with osmium tetroxide to afford the diol, which was protected as the acetonide to afford **148**. Treatment of **148** with potassium iodide and 18-crown-6 afforded the iodide **149**. This was then converted into the acetate 150, deacetylation of which gave the acetonide **153**. Removal of the acetonide **152**, and hydrolysis of the ester gave (-)-5-homo shikimic acid **154**. Disulphonimide **148** was also converted into the *O*-formyl derivative **151**, which was deprotected to give **152**.



(a) oxidation or fermentation. (b) CH_2N_2, MeOH-$(C_2H_5)_2O$, -20°C.
(c) TBDMSCl, imidazole, DMF, rt, 6h. (d) Ph_3CH_2, THF, reflux
(e) tetrabutylammonium fluoride, THF, 0°C, 3h. (f) MCPBA, Na_2HPO_4, CH_2Cl_2, reflux, 19 h (g) $NaBH_3CN$, BF_3-etherate, 5°C, 30 min.
(h) saponification (i) $(CH_3O)_2$.PO.Cl, pyr, 0°C, 1h. (j) TMSBr, CH_2Cl_2, 0°C, 1h. (k) NaOH, H_2O, 0°C, 4h - anion exchange chromatography

Scheme 1.36



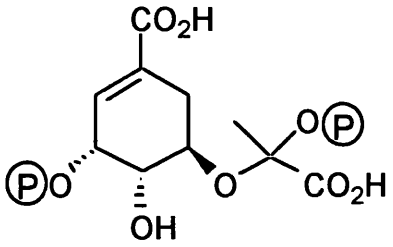
(a) PhMe, reflux; (b) $(TMS)_2NLi$, THF, -78^{0}C; (c) TFA; (d) NsCl, Et_3N, THF;(e) NaH, NsCl, DMF; (f) OsO_4, NMO;(g) $Me_2C(OMe)_2$, Me_2CO, p-TSA;(h) KI, 18-crown-6, PhMe,reflux, 7 days; (i) NaOAc, DMF, 110^{0}C, 2.5 h;(j) KI, DMF, 130^{0}C, 21 h; (k) aq. NH_3, MeOH, 48 h; (l) Amberlyst-15, MeOH, 20^{0}C, 17 h; (m) 50% aq. AcOH, THF, 60^{0}C, 3.5 h; (n) 50% aq. AcOH, THF, 60^{0}C, 17 h; (o) NaOH, H_2O, 20^{0}C, 5.5 h.

Scheme 1.37

1.4.2 Synthesis of 5-EPS-3-P Synthase Inhibitors

Bartlett *et al.* have synthesised a number of analogues[81,82] of the unstable tetrahedral intermediate **12**, that is involved in the 5-EPS-3-P reaction. Stable analogues of this high energy intermediate would be expected to benefit from the extra binding affinity that these species (and transition state structures) experience.[83,84]

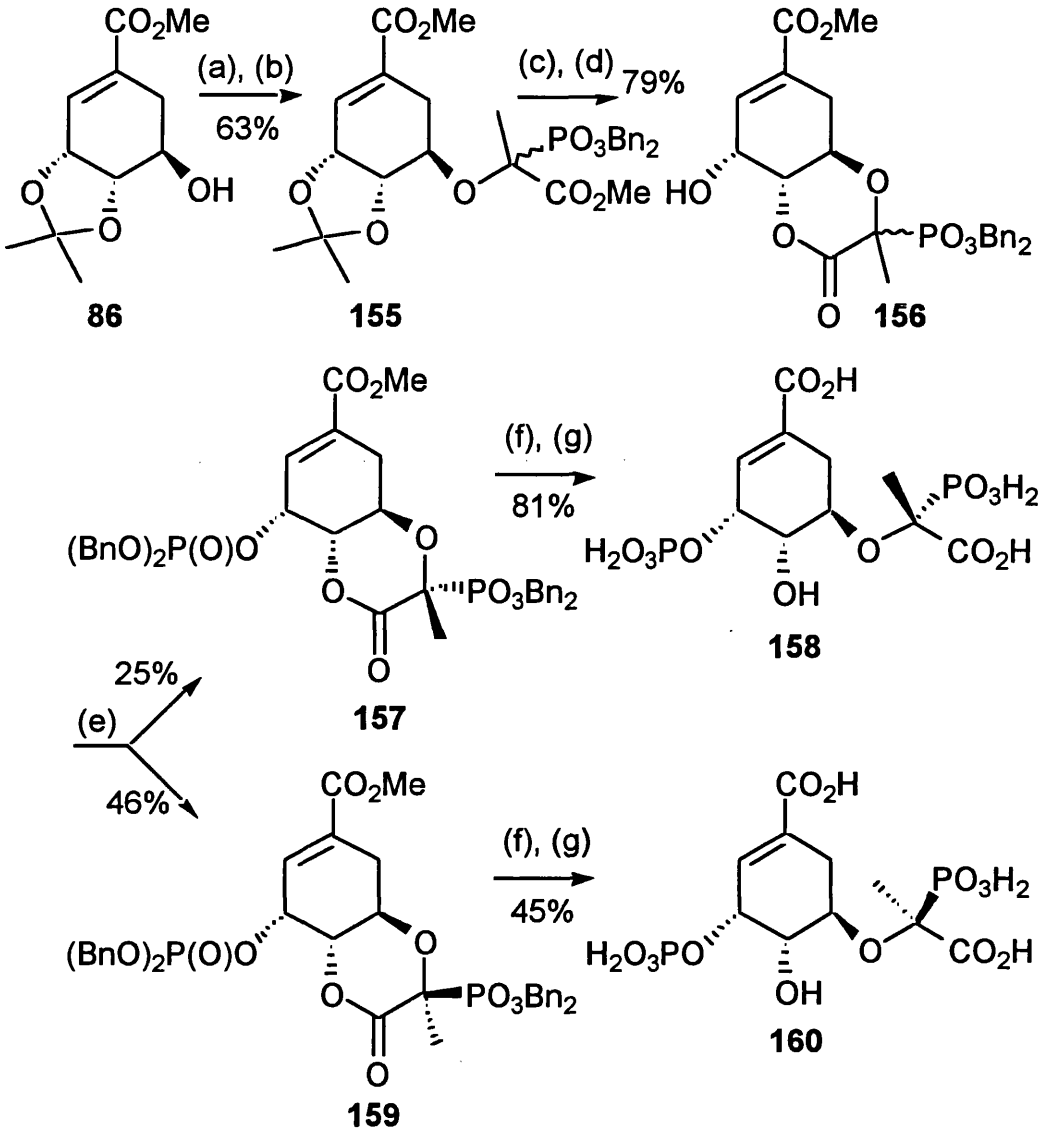
In order to try to stabilise the ketal phosphate structure of the intermediate **12**, the first group of analogues replaced the phosphate with a phosphonate. Phosphonates have been shown to bind more tightly than homophosphonates, when used as replacements for phosphates.[85]



12

The diastereomeric phosphonates were synthesised from the acetonide of (-)-methyl shikimate **86** (**scheme 1.38**). The $Rh_2(OAc)_4$ catalysed coupling of **86** with methyl (dibenzylphosphono) diacetate, followed by methylation, afforded the phosphonates **155**. Deprotection and cyclisation gave the lactones **156**, which were phosphorylated prior to separation **157**, **159**. Deprotection of both diastereomers yielded the phosphonate analogues **158** and **160**, which were purified as their sodium salts. Both phosphonates **158** and **160** were shown to be competitive inhibitors of 5-EPS-3-P synthase, with respect to 5-EPS-3-P, with binding constants K_i of 0.015 μM and 1.1 μM respectively. Compound **158** is the most potent inhibitor of 5-EPS-3-P synthase yet reported, binding more than a magnitude greater than the commercial herbicide glyphosphate. Since compound binds **158** much tighter than **160**, it was

suggested that this infers that the side chain of the natural intermediate **12** also has the same absolute configuration.

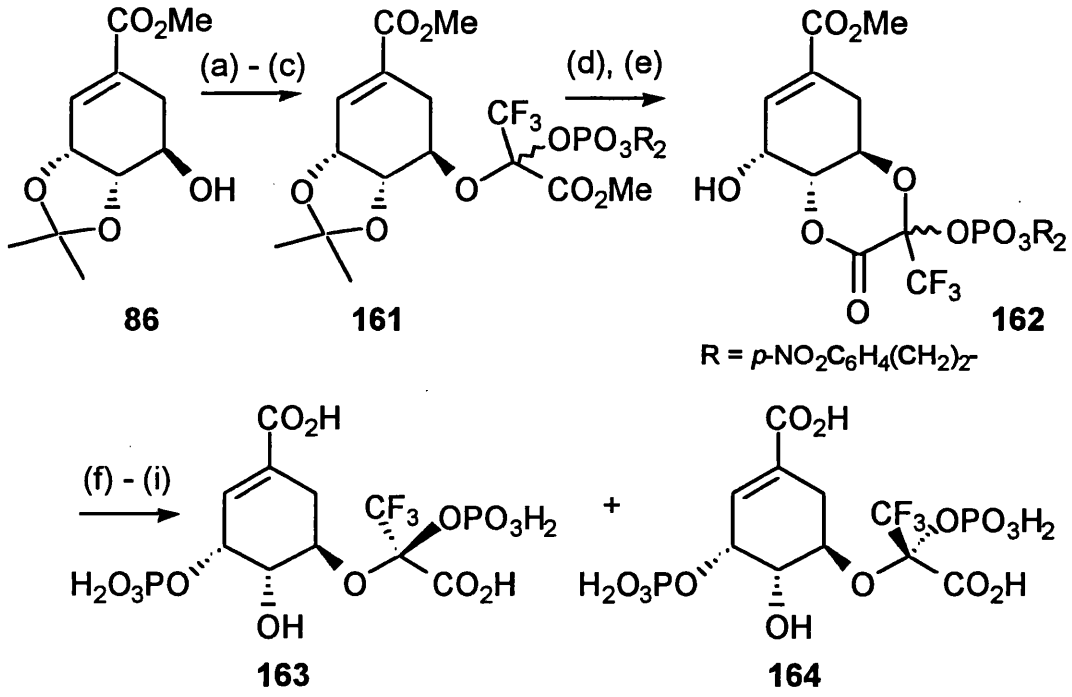


(a) $(BnO)_2P(O)C(N_2)CO_2Me$, $Rh_2(OAc)_4$, PhH, reflux; (b) KH, MeI, THF; (c) *p*-TSA, aq. MeCN; (d) *p*-TSA, PhH, reflux; (e) LDA, $[(BnO)_2P]O$, THF -78 to 10^0C; (f) TMSBr; (g) aq. NaOH.

Scheme 1.38

The second series of analogues involved the introduction of electron-withdrawing groups onto the methyl group of **12**, in order to destabilise the oxacarbonium ion that is presumably involved in the decomposition process. The trifluoropyruvate phosphate analogues were synthesised from the acetonide of (-)-methyl shikimate **86** (**scheme 1.39**). Reaction of **86** with methyl trifluoropyruvate

gave the hemiketal, which was phosphorylated to afford the diastereomeric phosphates **161**. Formation of the lactone **162**, further phosphorylation and deprotection, as before, yielded the trifluoromethyl analogues **163** and **164**. Both **163** and **164** were competitive inhibitors of 5-EPS-3-P synthase, with respect with to 5-EPS-3-P, with binding constants of K_i of 0.026 μM and 0.032 μM respectively. Due to these binding affinities being almost identical, doubt is cast over the earlier suggestion (see above) that the absolute configuration of the tetrahedral intermediate **12** can be determined from the differing affinities of the phosphonate analogues.

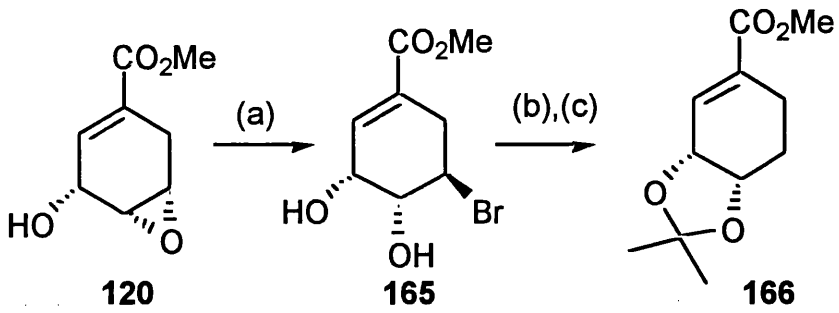


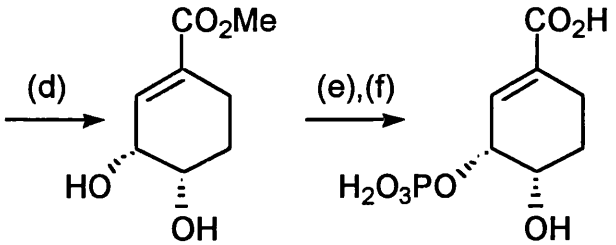
(a) $CF_3C(O)CO_2Me$, PCl_3; (b) *p*-$NO_2C_6H_4(CH_2)_2OH$; (c) *m*-CPBA; (d) H_3O^+; (e) K_2CO_3; (f) $[NO_2C_6H_4(CH_2)_2O]_2PNi(Pr)_2$; (g) *m*-CPBA; (h) DBU, BSA; (i) aq. NaOH.

Scheme 1.39

To probe the enzyme binding site of 5-EPS-3-P synthase, Anderson, Knowles *et al.*[86] have synthesised two inhibitors. The 5-deoxy derivative of shikimic acid-3-phosphate **168** was developed via Berchtold's epoxide[59] **120** (**scheme 1.40**). The epoxide was opened with dilithiumtetrabromonickelate to give

the bromoshikimate **165**, and was protected to give the acetonide. Tributyl tin hydride reduction **166**, followed by deprotection yielded the diol **167**. Hydrolysis and phosphorylation gave **168**, a modest inhibitor of 5-EPS-3-P synthase (K_I = 51 μM).



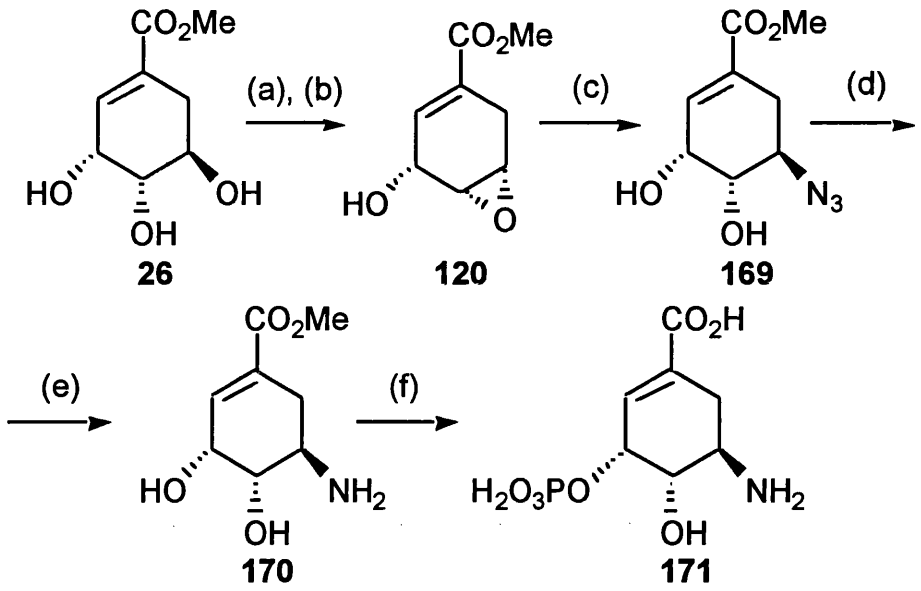


(a) Li_2NiBr_4, THF; (b) CH_2=C(OMe)Me, *p*-TsOH; (c) Bu_3SnH, AIBN, benzene; (d) Dowex 50W-X8 (H^+), MeOH; (e) aq. KOH, THF; (f) ATP, shikimate kinase.

Scheme 1.40

The 5-amino derivative **171** was also synthesised from (-)-methyl shikimate **26** via Berchtold's epoxide **120** (**scheme 1.41**). This time the epoxide was opened with sodium azide **169**, and after being reduced afforded the 5-aminoshikimate **170**. Hydrolysis and phosphorylation as before gave **171**, which was a similar inhibitor (K_i = 22 μM).

Campbell, Sainsbury *et al.* have recently synthesised the 5-methylene analogue of 5-enolpyruvyl shikimate **176** (**scheme 1.42**).[87] Starting from **149** (see **scheme 1.37** for synthesis)[80], this was coupled with the anion of methyl 3-nitropropanoate[88] to afford the nitro compound **172**. The reaction was carried



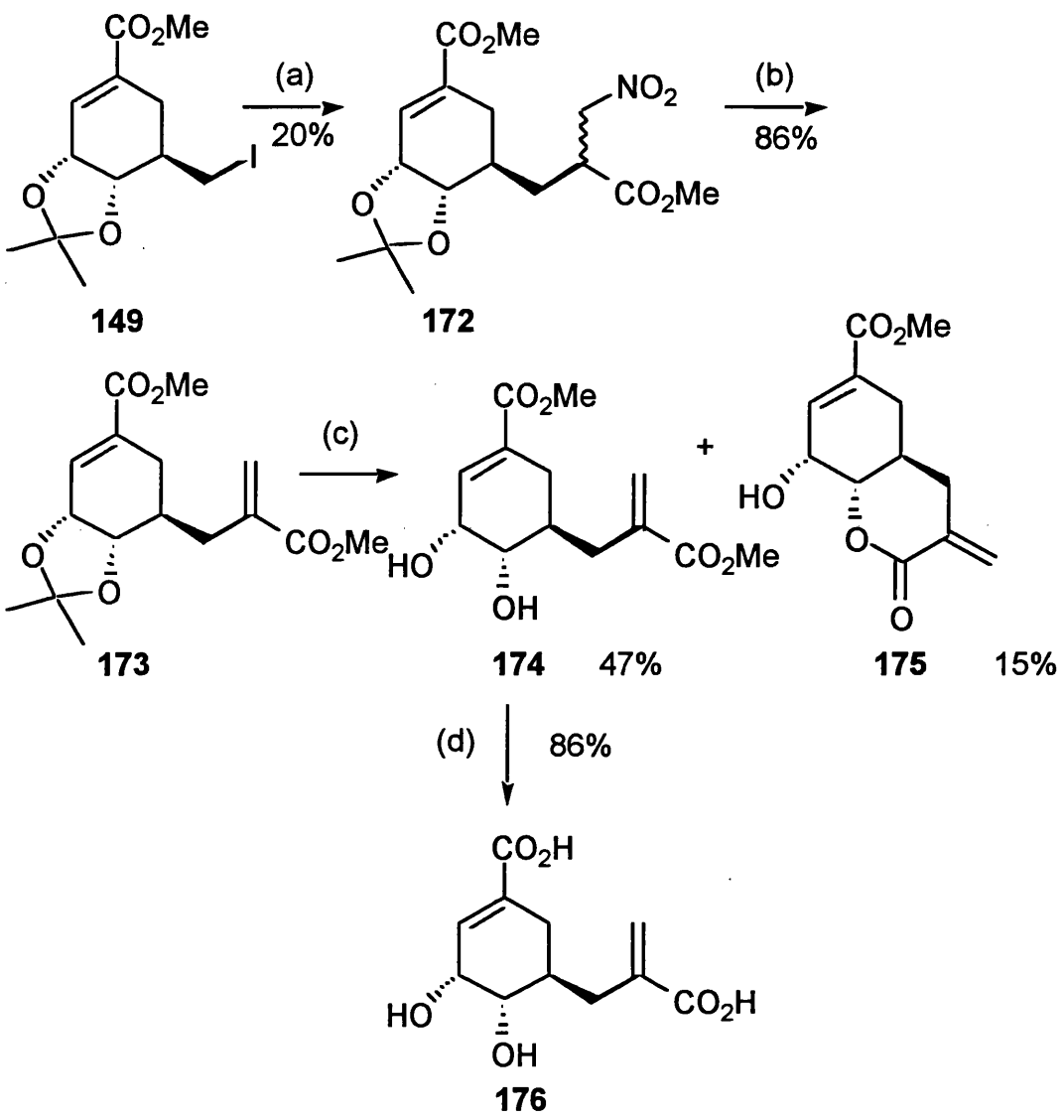
(a) Ph_3P, DEAD, THF; (b) 120^0C, 0.5 mmHg; (c) NaN_3, NH_4Cl, MeOH, H_2O; (d) H_2, Lindlar cat., EtOH; (e) aq. KOH, THF; (f) ATP, shikimate kinase.

Scheme 1.41

out in a 2:1 mixture of THF-DMPU in order to stabilise the dianion. Although the reaction was low yielding, the bulk of the recovered material was starting material **149**.

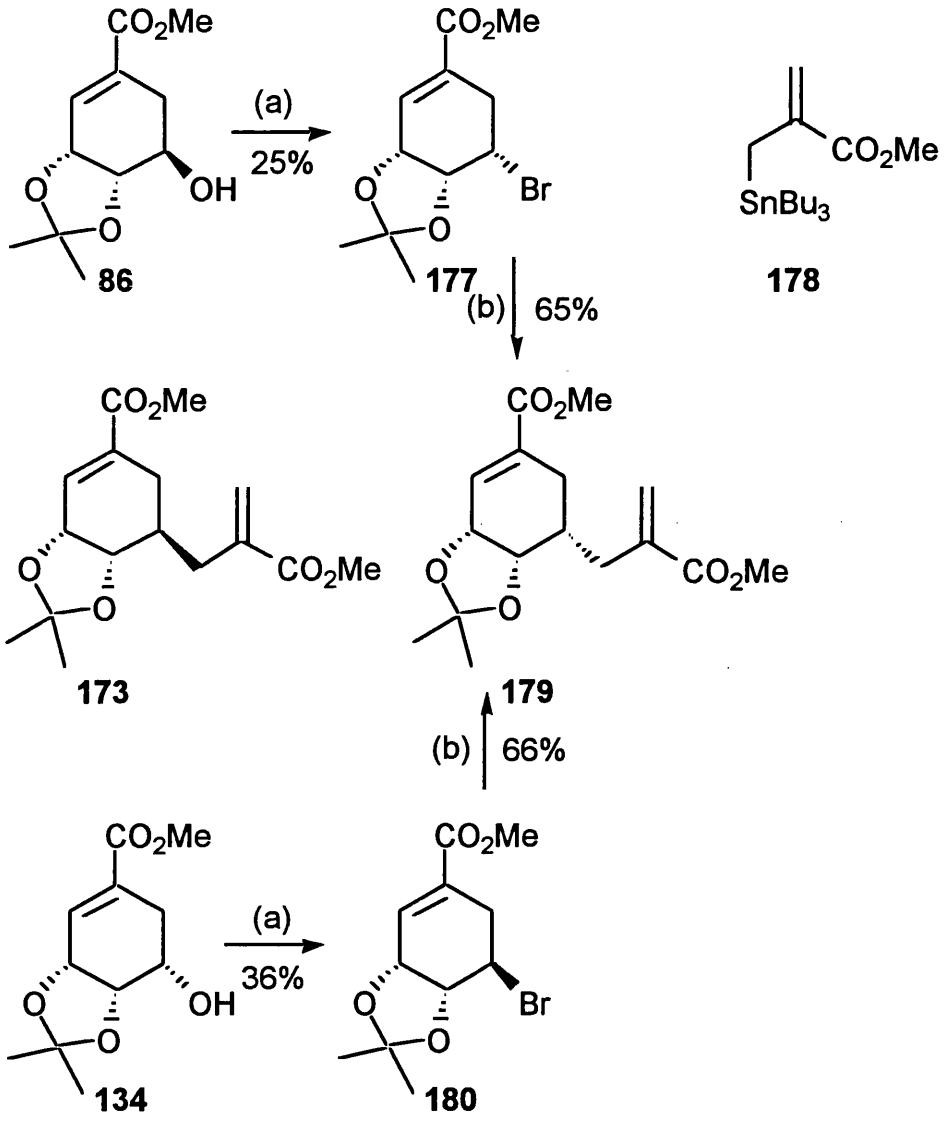
Nitro compound **172** was then treated with DBU which effected a clean elimination of nitrous acid, to yield the dialkene **173**. Deprotection of the acetonide group with aqueous acetic acid, afforded the diol **174**, and a small amount of the bicyclic lactone **175**. Diol **174** was then saponified to afford the diacid **176**, which is the carba analogue of 5-enolpyruvylshikimic acid **98**.

Another route to the protected carba analogue of 5-enolpyruvylshikimic acid **173**, has been published by Campbell, Sainsbury *et al.*[87] This synthesis used the acetonide of (-)-methyl shikimate **86**, or methyl 3α,4α-isopropylidenedioxy-5α-hydroxycyclohex-1-ene-1-carboxylate **134** as the starting material. Conversion of **86**



(a) $NO_2(CH_2)_2CO_2Me$, 2 equiv. LDA, THF,DMPU, -78 to 0^0C, 13 h; (b) DBU, THF, 20^0C, 4h; (c) 50% aq. AcOH, THF, 60^0C, 36 h; (d) NaOH, H_2O.

Scheme 1.42

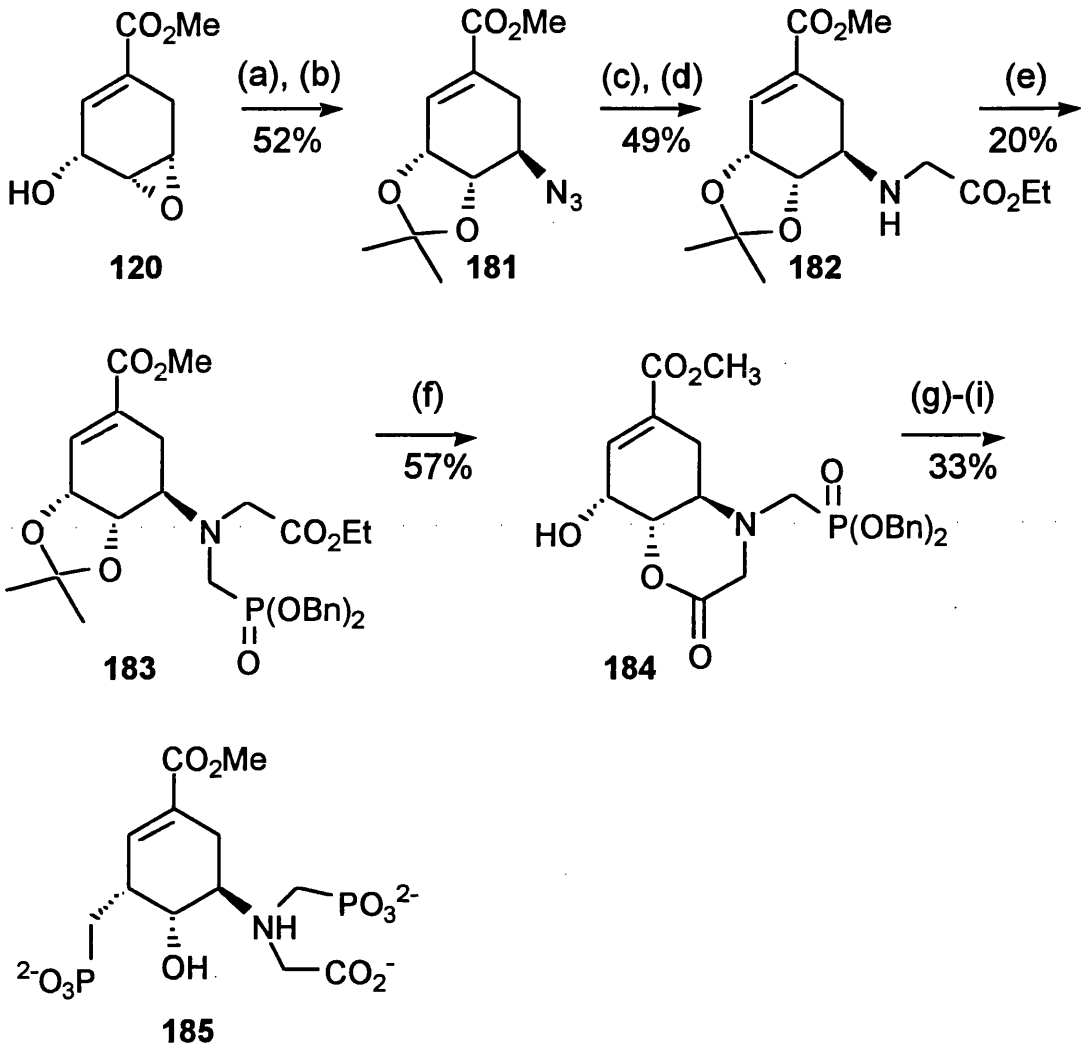


(a) CBr_4, PPh_3, THF, reflux; (b) AIBN, PhMe, reflux

Scheme 1.43

and **134** to their respective bromides **177** and **180** was accomplished by treating them with triphenylphosphine, carbon tetrabromide in THF.[89] The bromides **177** and **180** were then reacted with allylstannane **178**[90,91] to afford **173** and **179**.

Sikorski *et al.* have reported the synthesis of a 5-EPS-3-P synthase inhibitor based on its ternary complex with shikimate-3-



(a) NaN_3, NH_4Cl, H_2O-MeOH, reflux; (b) 2,2-dimethoxypropane, p-TSA; (c) H_2, MeOH, 5 % Pd/C; (d) $BrCH_2CO_2Et$, Et_3N, THF; (e) $(BnO)_2PO$-CH_2OTf, CH_2Cl_2, sat. $NaHCO_3$, reflux; (f) Dowex (H^+), H_2O-CH_3CN, reflux; (g) $(BnO)_2PO_2PO(OBn)_2$, $(Me_3Si)_2NNa$, THF, -78^0C; (h) TMSBr, (i) aq. NaOH, ion-exchange chromatography

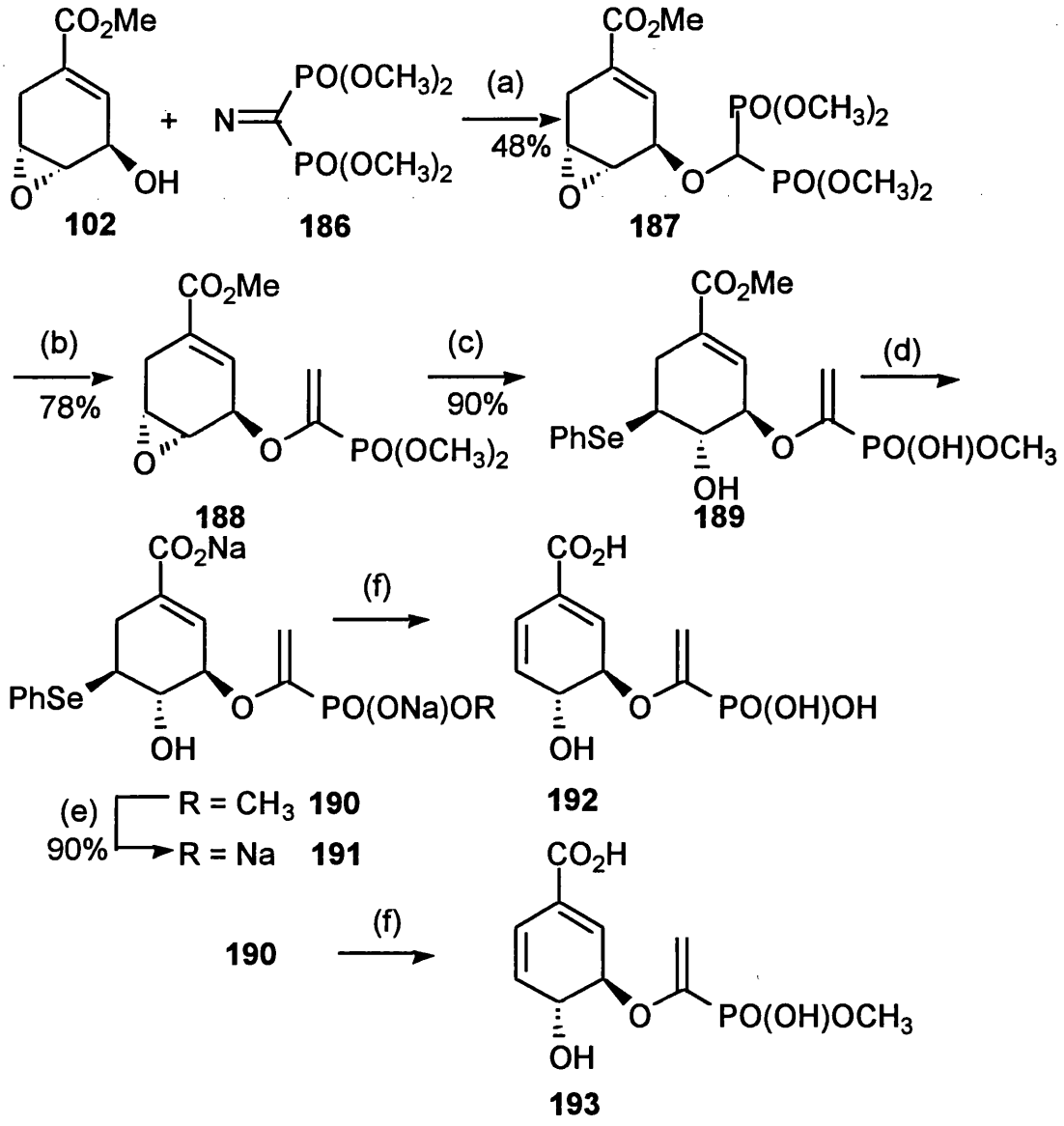
Scheme 1.44

phosphate and glyphosate **122** (**scheme 1.44**).[92] Epoxide **120** was opened with sodium azide,[93] and protected as the acetonide to give **181**. Hydrogenation using Lindlar's catalyst afforded the protected diol amine, which was alkylated with ethyl bromoacetate to give **182**. Alkylation of **182** with dibenzylphosphonomethyltriflate yielded **183**, which has the protected glyphosate functionality. Deprotection with Dowex resin yielded bicyclic lactone **184**. Phosphorylation of **184** with

tetrabenzylpyrophosphate, removal of the protecting groups with TMSBr, aqueous base and ion-exchange resin afforded **185**.

1.4.3 Synthesis of Inhibitors of Chorismic Acid

Ganem *et al.* have synthesised phosphonate analogues of chorismic acid **192** and **193** (**scheme 1.45**)[94] Epoxide **102** was reacted



(a) $Rh_2(OAc)_4$, PhH, reflux; (b) LHMDS, THF, -20^{0}C, CH_2=O; (c) $(PhSe)_2$, CH_3OH; (d) aq. NaOH; (e) TMSBr, py, CH_2Cl_2, aq. NaOH; (f) 30% H_2O_2, CH_3OH, 5^{0}C, 3,5-dimethoxyaniline, 20^{0}C.

Scheme 1.45

with tetramethyl methylenediphosphonate **186** to yield ether **187**. Horner-Emmons olefination of **187** using $LiN(TMS)_2$/ formaldehyde / THF furnished monophosphonate **188.** Opening of the epoxide of **188** with phenylselenide afforded **189**. Saponification of **189** yielded **190**. Treatment of **190** with TMSBr, aqueous base workup yielded trisalt **191**. Oxidation of **191** with hydrogen peroxide, and in *situ* selenoxide elimination with 3,5-dimethoxyaniline afforded **192**.

Phosphonate **193** was also synthesised from **190**, by a similar route. Saponification of **190** followed by oxidative elimination of the phenylselenide group, as before, afforded phosphonate **193**.

CHAPTER TWO

RESULTS AND DISCUSSION

2.1 Aims and Objectives

The primary objective of this project was to synthesise carba analogues of 5-EPS and chorismic acid, replacing the oxygen at the 3' position of the natural substrates **8** and **9** with a methylene group.

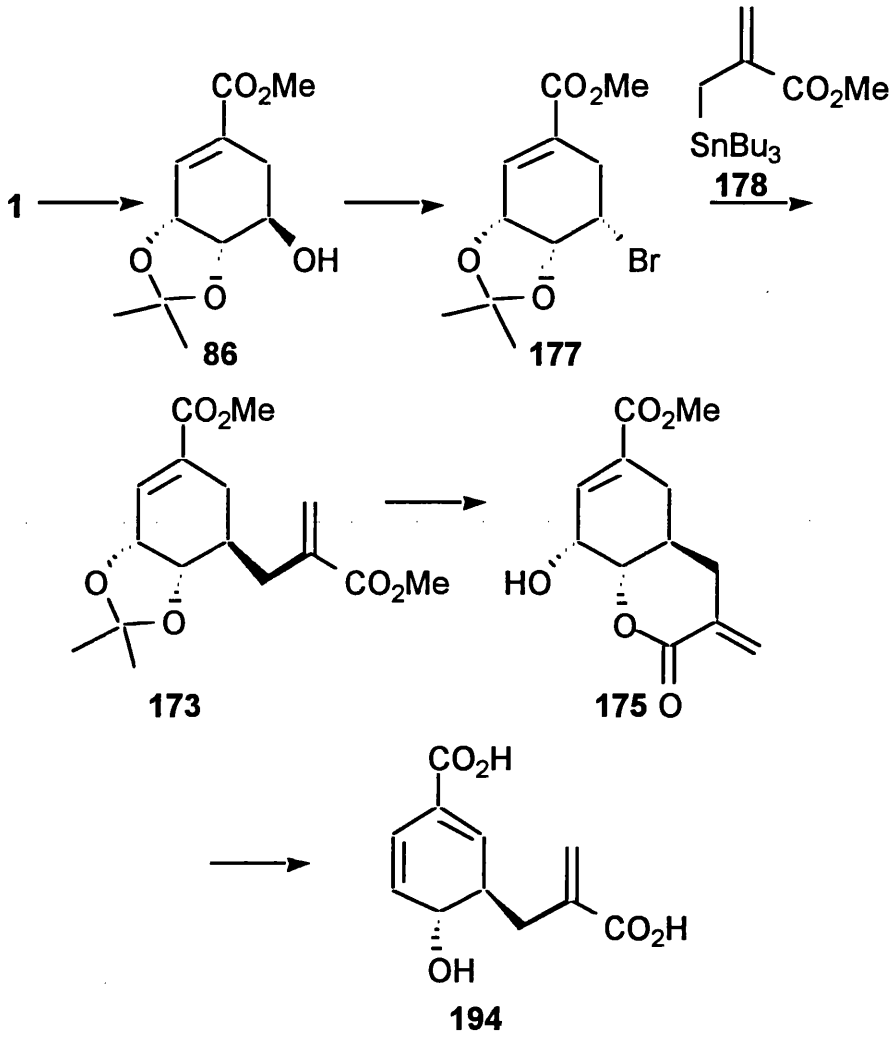
The synthesis of the carba analogue of 5-enolpyruvylshikimate has been demonstrated within the Bath laboratory via two separate routes (**section 1.4.2, schemes 1.42 and 1.43**).[87] Starting from (-)-shikimic acid **1** it was envisaged that the second route (**scheme 2.1**) would lead to 5-homoshikimate **173** and from there to bicyclic lactone **175**. This could hopefully then be manipulated to give 5-homochorismic acid **194**.

2.2 Synthesis of 5-α-Bromoshikimate

It was decided that we would synthesise the secondary alkyl bromide **177** in the same way that has already been reported from within the Bath group (**section 1.4.2 scheme 1.43**).[87]

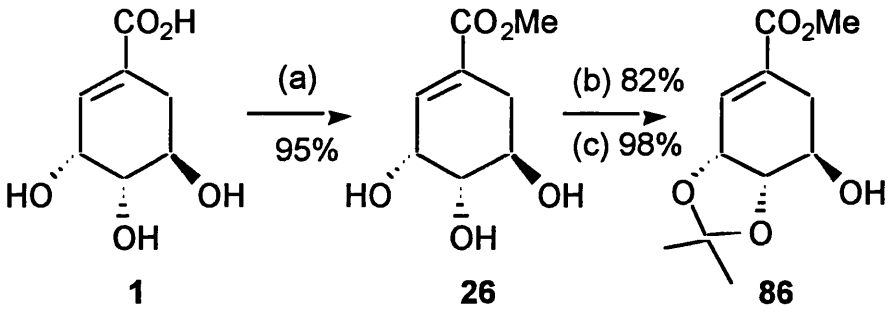
2.2.1 Protection of Shikimic Acid

(-)-Shikimic acid **1** was protected as the methyl ester **26** by bubbling HCl(g) into a solution of shikimic acid in methanol until the solution was saturated.[95] The product was formed in good yields, upto 95%. The 3,4-*cis*- diol was then protected by conversion to an acetonide **86**, by treatment with 2,2-dimethoxypropane and



Scheme 2.1

acetone. Although the yields in the reaction were in the order of 82%, when 2,2-dimethoxy propane was used in a 5-10 fold excess, without any acetone being present, the reaction was complete after only fifteen minutes and the yield was 98% **(scheme 2.2)**.[58] Analysis by ^{1}H n.m.r. shows the presence of two singlets at δ= 1.41 p.p.m. and at δ= 1.45 p.p.m., peaks which correspond to the resonances of the gem dimethyl unit of the acetal.



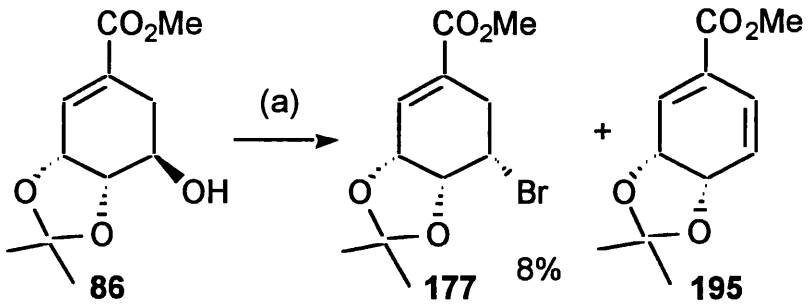
(a) $HCl_{(g)}$, MeOH; (b) 2,2-dimethoxypropane, $Me_2C=O$, *p*-TSA, 4 h; (c) 2,2-dimethoxypropane (5 equiv.), *p*-TSA, 15 min.

Scheme 2.2

2.2.2 Bromination at C-5

It was hoped to achieve formation of the secondary alkyl bromide **177** by treatment of **86** with triphenylphosphine and a tetrahalomethane. Such reactions are known to proceed both with high conversion and in high yields,[96] plus with extensive inversion of configuration.[97]

A mild and rapid procedure for the preparation of alkyl bromides from alcohols, as reported by Hooz and Gilani[89,98] and as used in our laboratory previously, was employed to obtain the 5α - bromo compound (**177**) (**scheme 2.3**).



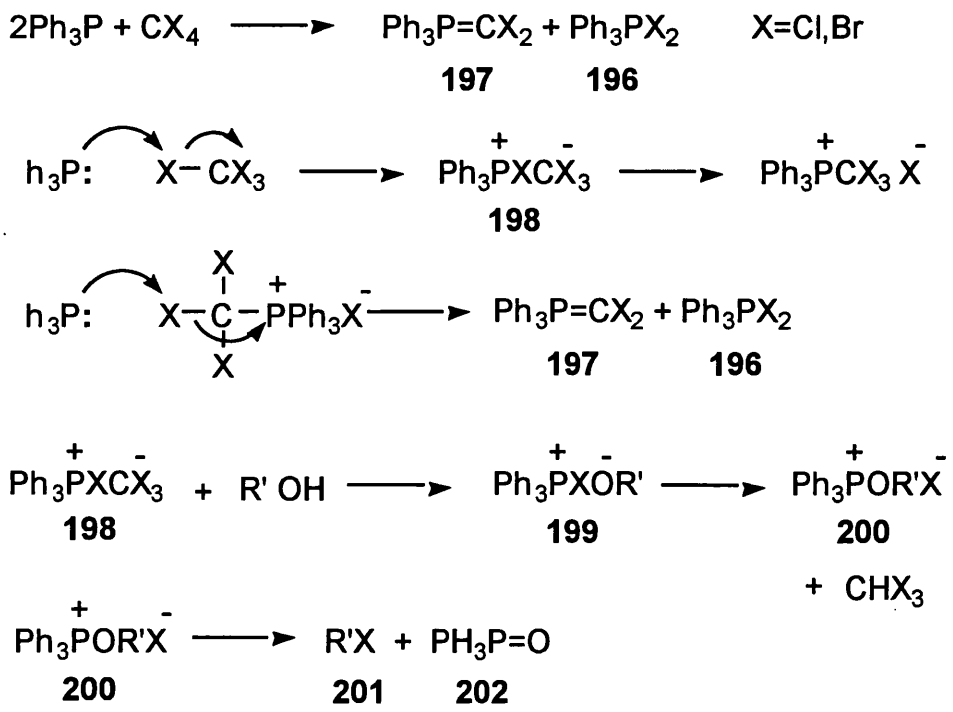
(a) CBr_4, Ph_3P, THF, reflux

Scheme 2.3

Reagents of the type R_3PX_2 (where R=Ph or n-Bu and X=Cl or Br) have been demonstrated to permit the conversion of alcohols to alkyl halides without the complication of elimination or rearrangement.[99] The exclusion of elimination reactions was particularly important because the loss of HBr from **177** is facile.[34, 89] The driving force for this is the thermodynamic stability of the corresponding diene **195**. The mechanism of the elimination is undetermined, since a trans - diaxial arrangement for the loss of HBr is not possible.

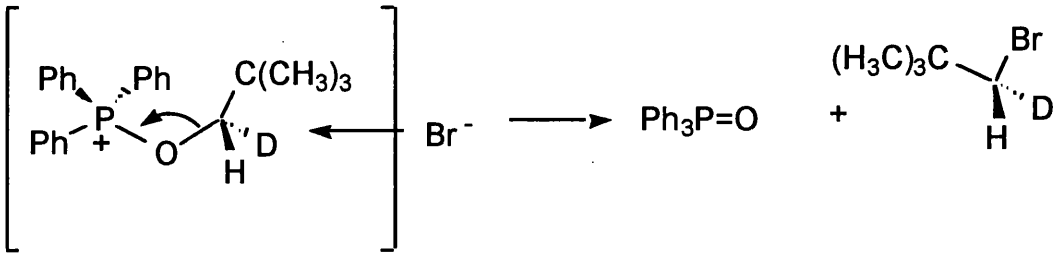
It has been demonstrated that the interaction of triphenylphosphine with carbon tetrahalides results in the formation of triphenyl phosphine dihalide **196** and an ylid **197**.[100] An ionic mechanism to account for this is shown as **Scheme 2.4**. The intermediate **198** can be trapped by alcohols to form **199** or **200**, which then collapse to give triphenylphosphine oxide **202** and an alkyl halide **201**.

Two possible ways by which the salt **200** may decompose have been outlined by Franzus *et al.*[101]



Scheme 2.4

(i) A first-order decomposition of a cluster of intimate ion pairs, which is stabilised by the interaction of a positively charged phosphorus atom with an adjacent negatively charged bromide ion (**scheme 2.5**).



Scheme 2.5

(ii) A σ2s + σ2a thermal pericyclic reaction, where the P-Br bond is broken suprafacially and the C-Br bond is made antarafacially.

All the kinetic, energetic, stereochemical and isotopic data are consistent with the ion-pair mechanism (i).

Acetonide **86** was reacted with carbon tetrabromide and triphenylphosphine in refluxing THF for five hours (**scheme 2.3**). This reaction was also attempted with dry THF as the solvent with very little success, just resulting in mainly starting material, some of the by-product triphenylphosphine oxide **201**, and a small amount (8%) of the required 5α-bromo compound **177**. The latter was obtained as an oil, which crystallized on standing to give colourless needles. A second product was also isolated from the reaction mixture. This had a lower R_F (0.23) than the desired product (R_F 0.61) (petrol-ethyl acetate 4:1), but was only obtained in a very low yield (2%).

Analysis by ^1H n.m.r. showed it to be the diene **195** (**scheme 2.3**) (previously synthesised by Bowles[34]), which forms by the elimination of HBr from **177**. This has characteristic peaks at δ= 6.04 p.p.m. and at δ= 6.54 p.p.m. corresponding to the resonances of the allylic protons at C-5 and C-6, respectively. Analysis by ^1H n.m.r. of 5α -bromo **177** showed that the chemical shift of the 6β proton had moved from

δ= 2.25 p.p.m. in compound **86** to δ= 2.97 p.p.m. This is due to the presence of the 5α-bromine atom (**table 2.6**).

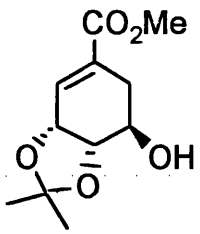
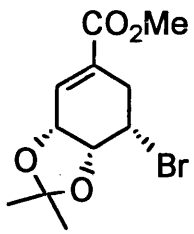
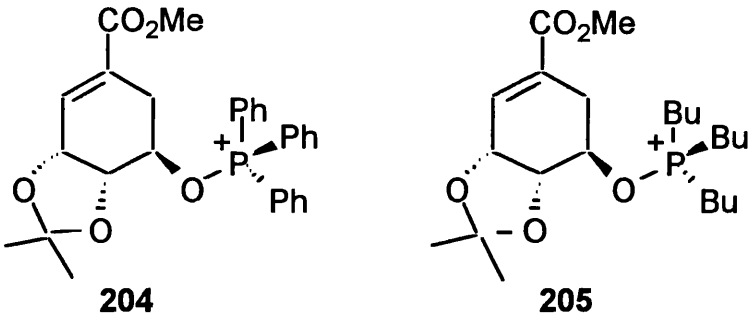
Proton Resonance	**Chemical Shift (δ)**	
	 **86**	 **177**
6β-H	2.25	2.97
6α-H	2.80	2.83
5-H	3.91	4.18
2-H	6.92	6.76

Table 2.6

but this was unsuccessful. We considered that perhaps either a very small amount of water, or exceptionally dry conditions, might help the reaction but neither did. Thinking that the steric bulk of the intermediate **204** (**figure 2.7**) might hinder the reaction, we replaced triphenylphosphine with tributylphosphine. In addition, the latter reagent is more nucleophilic and so the intermediate would localise the positive charge on phosphorus facilitating the nucleophilic attack of Br^-.[102] Our expectation was partly fulfilled and the yield was now increased to 15%, but this was still not as good as that quoted.[87,103]



204 **205**

Figure 2.7

Another reaction, in which the secondary hydroxyl group of **86** could be replaced by a bromine atom, was sought. One method investigated involved the *in situ* formation of dibromotriphenylphosphorane[98b], made by adding bromine to a mixture of the alcohol **86**, triphenyl phosphine and THF. We added bromine dropwise until two drops gave a slight orange tint to the solution. However, after stirring the reaction mixture we had no evidence (by tlc) that anything had happened. The solution was then warmed resulting in an orange solution but again no product formed and starting material was recovered.

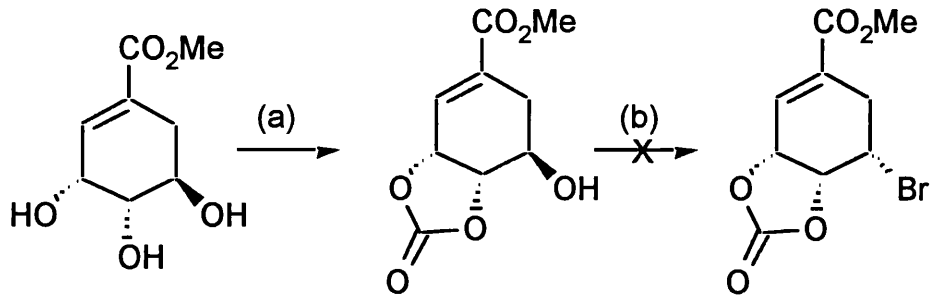
This reaction was repeated using pre-formed dibromotriphenylphosphorane. This too failed to react with **86** and so another similar reaction was tried. This time this required the use of N-bromosuccinimide (NBS) and triphenylphosphine.[104] A solution of NBS in THF was treated dropwise with a solution of triphenylphosphine in THF. Acetonide **86** in dry distilled THF was then added and the reaction was stirred for four hours. Since no reaction had occurred the reaction was heated to reflux for a further 5 hours, but again only starting material was recovered.

This called for more drastic conditions and we used PBr_3 as the brominating agent.[105] Consequently a solution of **86** in DCM was treated dropwise with PBr_3 over fifteen minutes. The reaction was then stirred at room temperature overnight. Despite this no reaction occurred and so the reaction was heated to reflux for seven hours. At the end of this no reaction has occurred.

We attempted to carry out a standard reaction, namely O-silylation with trimethyl silyl chloride in the presence of lithium bromide.[106] This too failed and so it was clear that this function must be very sterically hindered and undoubtedly this is a feature of the acetonide unit.

Next a solution of acetonide **86** in dichloromethane was treated with triphenyl phosphine and 1,2-dibromotetrachloroethane. 1,2-Dibromotetrachloroethane was chosen as it is known to lead to a better formal leaving group than carbon tetra-bromide.[107] The reaction mixture was stirred at room temperature for forty minutes after which time no reaction had occurred. The reaction mixture was heated to reflux for ten hours but no product was seen by monitoring the reaction by t.l.c.

As the conversion of acetonide **86** to bromide **177** was proving so difficult to achieve, we decided to change the protection of the C-3, C-4 diol to try to reduce the steric bulk of the acetonide. Berchtold *et al.* have synthesised the cyclic carbonate **93**.[59] We decided to prepare **93** and then attempt to convert the free hydroxyl at C-5 into the bromide **206 (scheme 2.8)**.



26 **93** **206**

(a) N,N'-carbonyl diimidazole, THF, reflux; (b) (i) CBr_4, Ph_3P, THF, reflux; (ii) CBr_4, Bu_3P, THF, reflux; (iii) $(BrCl_2C)_2$, Ph_3P, DCM, reflux.

Scheme 2.8

Methyl shikimate **26** in dry THF was heated to reflux. To this was added N,N'-carbonyldiimidazole portion-wise over a five hour period.[108] The reaction was

heated to reflux for a further two hours and after work-up was shown to afford the cyclic carbonate **93** in 78% yield.

Product **93** in THF was treated with carbon tetrabromide and triphenyl phosphine and heated to reflux for 4 hours. Frustratingly no reaction occurred so we decided to replace triphenyl phosphine with tributyl phosphine as this had increased the yield with acetonide **86**, but in practise this failed to promote the desired reaction.

Reagents	Solvent	% Yield of 177
CBr_4, Ph_3P	THF	8
CBr_4, Ph_3P	DCM	9
CBr_4, Bu_3P	THF	15
Ph_3P, Br_2	THF	0
Ph_3PBr_2	THF	0
NBS, Ph_3P	THF	0
PBr_3	DCM	0
Me_3SiCl, LiBr	MeCN	0
$(BrCl_2C)_2$	THF	0
$(BrCl_2C)_2$	DCM	0

Table 2.9

Next carbon tetrabromide was replaced by 1,2-dibromo-tetrachloroethane in final bid to try to convert the carbonate **93** into the bromide **206**. A solution of

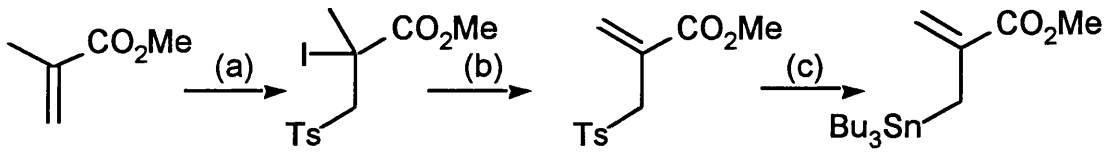
carbonate **93** in diethyl ether was treated with triphenyl phosphine and 1,2-dibromotetrachloroethane. The reaction mixture was heated to reflux for six hours but no product was forthcoming.

Although we had only been able to synthesise bromide **177** in low yield (**table 2.9**), we decided to carry on with the attempted synthesis of **173** and **175**, and then go back and attempt to optimise the route.

The next step in the proposed synthesis involved the introduction of the 2-methoxycarbonylprop-1-en-3-yl side chain at C-5, by a radical fragmentation reaction with an appropriate allylstannane.

2.3 Synthesis of Methyl 2-(tri-n-butylstannylmethyl)propenoate 178

The required allylstannane (**178**) has been synthesised by Baldwin *et al.* starting from methyl methacrylate **207** (**scheme 2.10**).[90]



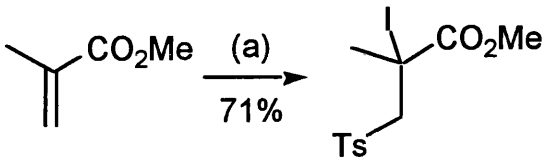
207 **208** **209** **178**

(a) I_2, *p*-toluenesulfinate hydrate, MeOH;
(b) Et_3N, DCM, reflux 8h;
(c) Bu_3SnH, AIBN, PhMe, reflux 1h.

Scheme 2.10

2.3.1 Formation of Methyl 2-iodo-2-methyl-3-(toluene-*p*-sulfonyl)-propanoate 208

The first step in the reaction to form the allylic tributyltin hydride side chain **178** was the addition of a *p*-toluenesulfonyl radical (Ts.) and iodine to the carbon-carbon double bond of methyl methacrylate **207** (**scheme 2.11**).[109]



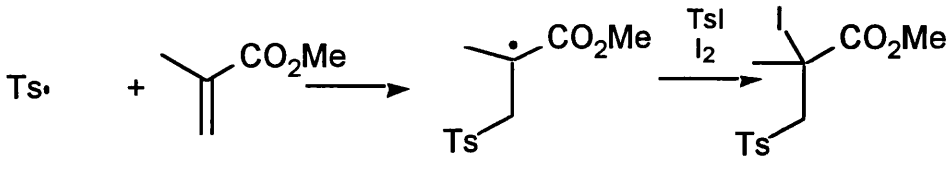
207 **208**

(a) MeOH, *p*-TsNa.2H_2O, I_2, 25°C, 2 h

Scheme 2.11

The first step in the formation of **208** is the production of *p*-toluenesulfonyl iodide, formed by the reaction between iodine and sodium *p*-toluenesulfinate hydrate. This is reactive enough to combine directly with alkenes in the daylight, without the addition of a catalyst, and undergoes spontaneous homolysis in DCM at room temperature, to give a *p*-toluenesulfonyl radical (Ts.).

The *p*-toluenesulfonyl radical (Ts.) acts as the chain carrier, initially reacting with the double bond to yield an alkyl radical which reacts rapidly with iodine (**scheme 2.12**).



207 **208**

Scheme 2.12

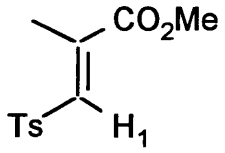
It has been established by Corrêa and Waters[110] that a heterolytic reaction of *p*-toluenesulfonyl iodide is not involved in this reaction by showing that

(i) there is little addition of *p*-toluenesulfonyl iodide to vinyl cyanide or to butadiene in the dark,

(ii) in daylight the addition to methylacrylate and vinyl cyanide is markedly retarded by the addition of the 'radical trap' quinol.

It is extremely unlikely that a Ts+ cation is involved in this type of reaction since the orientation of addition would be incorrect and in any case the alkene is electron-poor. Indeed, the Ts+ cation formed by treating *p*-toluenesulfonyl chloride with silver perchlorate or aluminium chloride does not add to methyl acrylate or vinyl cyanide.[110]

Methyl methacrylate **207** in dry distilled methanol was treated with two equivalents of iodine and two equivalents of *p*-toluenesulfenic acid sodium salt hydrate, and was stirred at room temperature for four hours. **208** was formed as a white crystalline solid in 71% yield. This was found to photo-decompose on standing to the yellow crystalline solid **210**, and hence it was kept in a darkened environment.

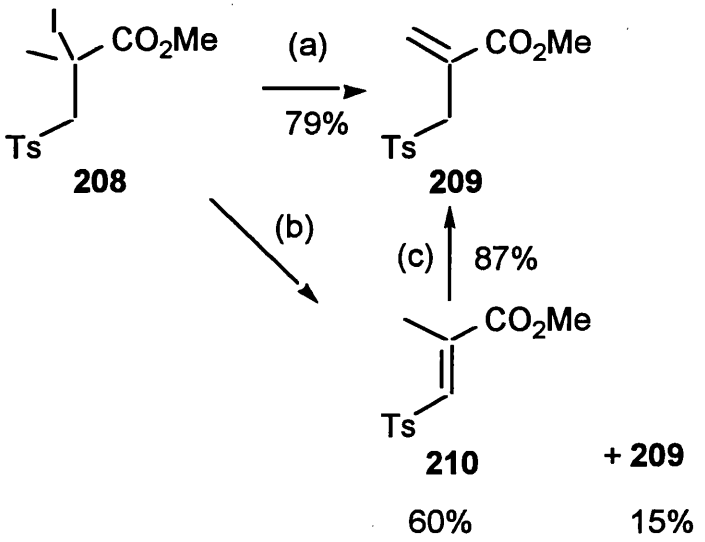


210

When the reaction was repeated but this time allowed to stir for 24 hours[111] alkene **210** was obtained as the only product in 55% yield. This is obviously formed as a result of decomposition of **208**. The ^1H n.m.r. spectrum of **210** exhibits a ^1H singlet at δ= 7.22 p.p.m., corresponding to the resonance of H_1, together with the appropriate resonances of the tosyl residue.

2.3.2 Formation of Methyl 2-((toluene-p-sulfonyl)methyl)propenoate 209

The next step of the synthesis was to form **209**, this is possible from either **208** or **210**. Elimination of HI was achieved by refluxing **208** or **210** with Et_3N in DCM (**scheme 2.13**).[112] The reaction was complete after 8 hours giving **209** in 79% yield. This conflicts with the results of another identical reaction where two products were formed, one being the more thermodynamically stable compound **210**. Indeed, the initial product of the reaction is **210**, which then rearranges under basic conditions to give the terminally double bonded species **209**.[109] Presumably **210** is more stable than **209**, because in the former the two electron withdrawing groups are deconjugated. By following the reaction by t.l.c. analysis, it was possible to see the gradual formation of the desired product **209** and the disappearance of **210**.



(a) Et_3N, CH_2Cl_2, reflux, 8 h; (b) Et_3N, CH_2Cl_2, reflux, 20 h;
(c) Et_3N, $CHCl_3$, reflux, 13 h;

Scheme 2.13

Purification of the reaction mixture afforded the required product **209** as a pale yellow viscous oil. The ^1H NMR showed two singlets at δ=6.49 ppm and δ=5.83 ppm corresponding to the signals of the olefinic protons 3-H' and 4-H'.

2.3.3 Formation of Methyl 2-(tri-n-butylstannylmethyl)propenoate 178

Tributyltin hydride is currently one of the most widely used reagents in organic synthesis, due mainly to its versatility as a free-radical reductant. The reaction of organotin hydrides with alkenes normally yield hydrostannylated species, which are useful as synthetic intermediates. However, when organotin hydrides are reacted with allylic sulfides or sulfones, the resulting product is an allyl stannane. This is an example of a $^{\bullet}$SH reaction, in which an organotin radical acts as the attacking species, with the consequent elimination of an organosulfur-centred radical.[113]

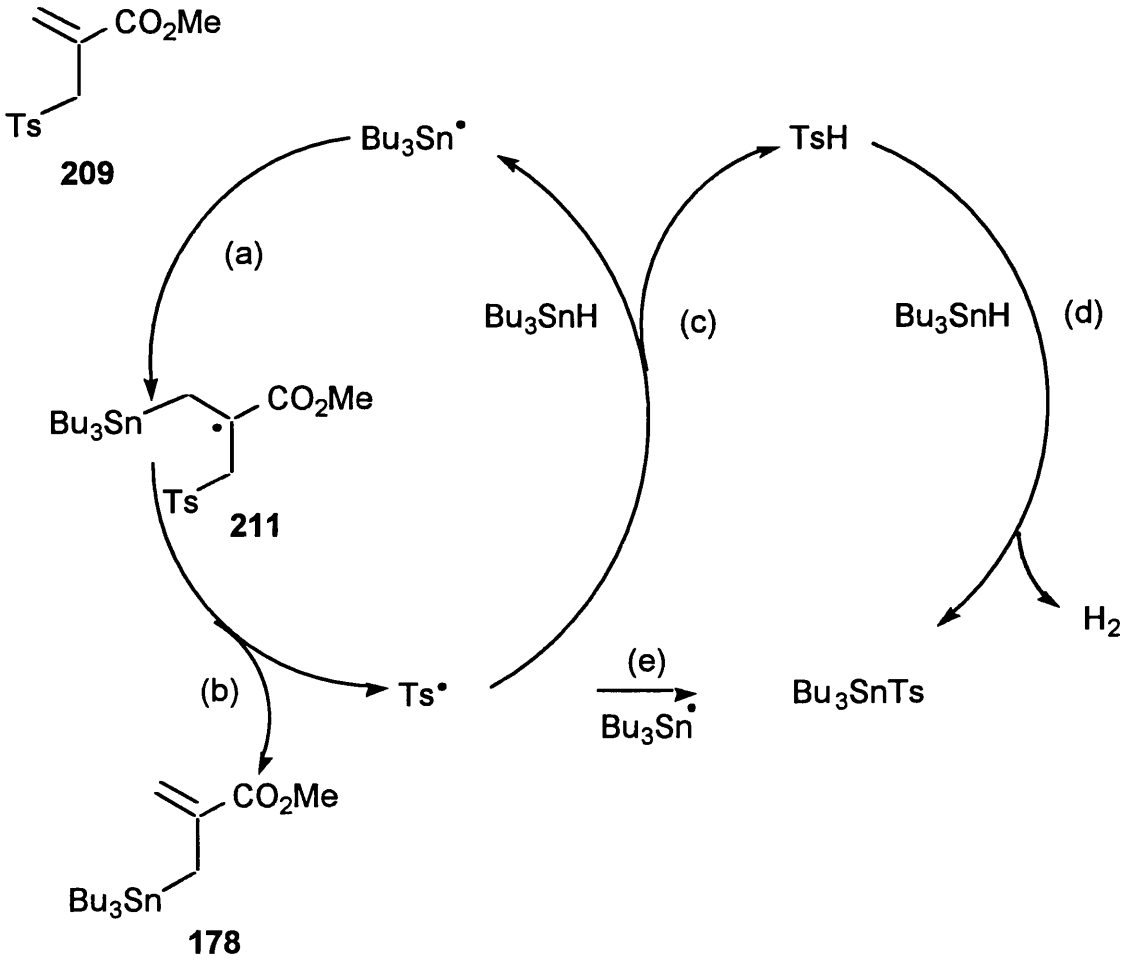
The key to the $^{\bullet}$SH stannylation reaction is the regiospecific allyl transfer from sulfur to tin, in which carbon-tin bond formation is achieved by a homolytic process. This is a synthetically useful reaction, as generally such allyl stannanes have been prepared by polar processes involving Grignard reagents or organostannyl lithium species. These are not viable methods for derivatives containing carbonyl or cyano functional groups.[112]

It has been shown by Sayer, Conlon *et al.* that the attack by the organotin radical is at the allylic double bond, and not a direct homolytic substitution (SH process) at the sulfur atom.[114] In experiments using propargyl sulfide and tributyltin hydride, the reaction mixture was found not to contain a mixture of acetylene and isomeric allene, which would have been expected if a direct SH process was in operation (**scheme 2.14**).

The next step in the formation of the allylstannane involves the reaction of **209** with tributyltin hydride (**scheme 2.15**),[90] followed by (b), the elimination of the *p*-toluenesulfonyl group from the product **211** formed in (a). The p-toluenesulfonyl radical reforms the tributyltin radical in a reaction with tributyltin hydride (c). This is relatively faster than either of the termination steps (d) and (e).

2.4 Methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonyl-prop-1-en-3-yl] - cyclo-hex-1-ene-1-carboxylate 173

The problem with conducting intermolecular reactions by the tin hydride method is that the initial radical **212** must add to an alkene **213** and not be trapped by tin hydride, whereas the adduct radical **214** must be trapped by tin hydride so generating tributyltin radical **215** and not add to the alkene (**figure 2.16**).[116] The tin hydride method can be synthetically useful only if the



Scheme 2.15

required reactions are faster than all the others. A fragmentation approach is a clever alternative that avoids this selectivity problem.[117] Here the tin is incorporated into the alkenic unit so that the net effect is substitution rather than reduction. Thus, chain

carriers (like $Bu_3Sn.$) are generated by a fragmentation rather than by an atom-transfer step. Fragmentation methods based on allyltrialkyltin reagents (**scheme 2.17**) are especially useful. These syntheses benefit from the rapid cleavage of

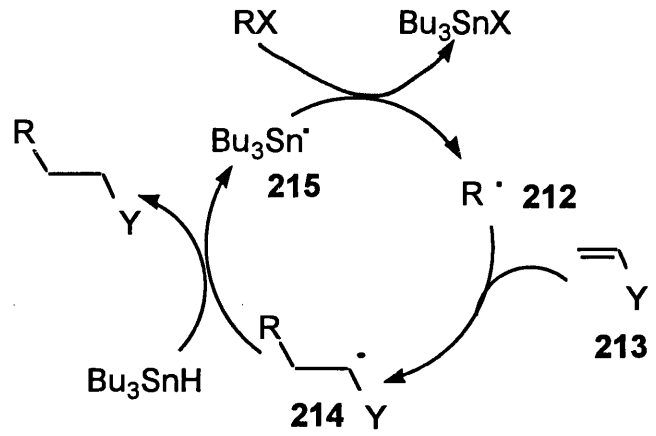
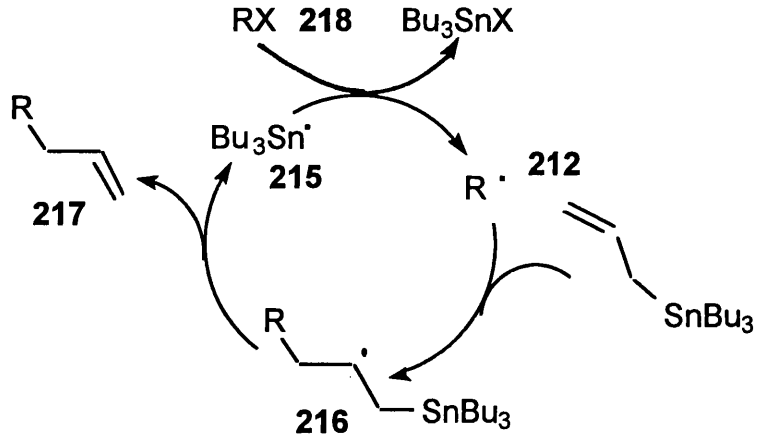


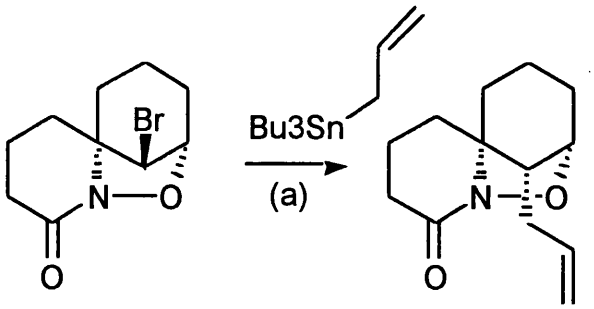
Figure 2.16

a C-Sn bond *beta* to a radical centre. Therefore, the adduct radical **216** gives an allylsubstituted product **217** by splitting off a tributyltin radical **215** that reacts with **218** to give **212**. Compound **218** can be a halide, xanthate, thioether or selenide.



Scheme 2.17

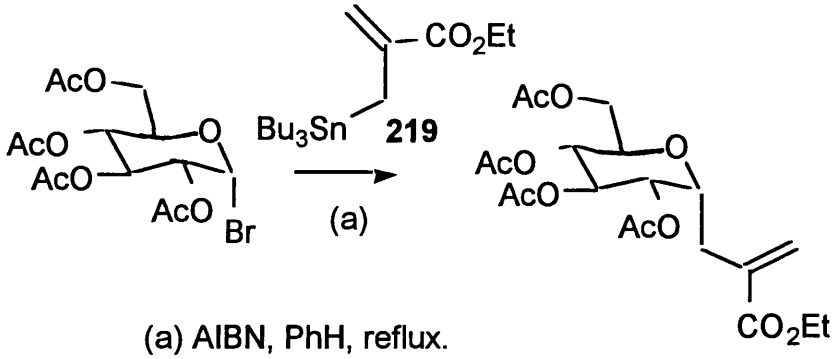
Keck *et al.* first applied such a method to the synthesis of (±)-perhydrohistrionicotoxin (**scheme 2.18**).[118]



(a) PhH, hν.

Scheme 2.18

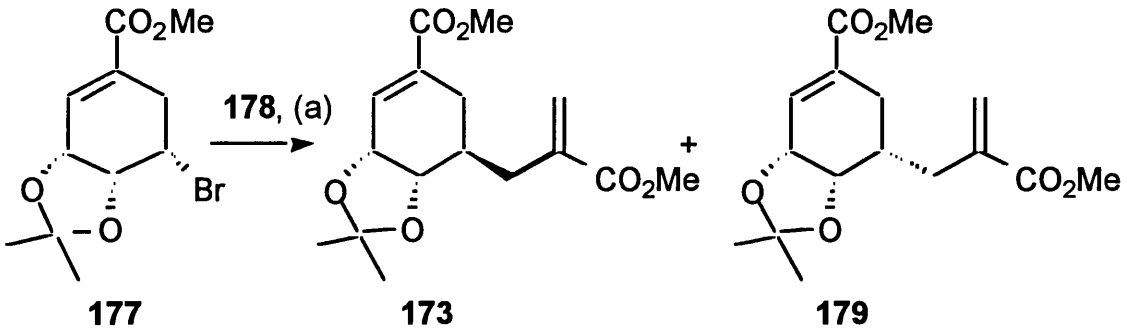
Giese *et al.* have recently used a similar stannane **219** to that used by us, as a synthon of phosphoenol pyruvate (**scheme 2.19**).[119]



(a) AIBN, PhH, reflux.

Scheme 2.19

A solution of bromide **177**, in degassed toluene, was treated with two equivalents of the allylstannane **178** and a catalytic amount of AIBN to afford the carba analogues of protected 5-enolpyruvylshikimate **173** and **179** (**scheme 2.20**).



(a) AIBN, toluene, reflux.

Scheme 2.20

Two products were observed by t.l.c. (R_F 0.38 and R_F 0.41 petrol/ethyl acetate 4:1) and were separated by column chromatography on silica gel. These were found by ^1H n.m.r. to be the 5-β **173** and 5-α **179** -diastereoisomers respectively . The spectrum of compound **173** shows distinctive peaks at δ= 5.56 ppm and δ= 6.24 ppm that arise from the resonances of the two protons at C-1'. For compound **179** these peaks are found at δ= 5.86 ppm and δ= 6.43 ppm. The coupling constants for **173** are shown in **figure 2.21**.

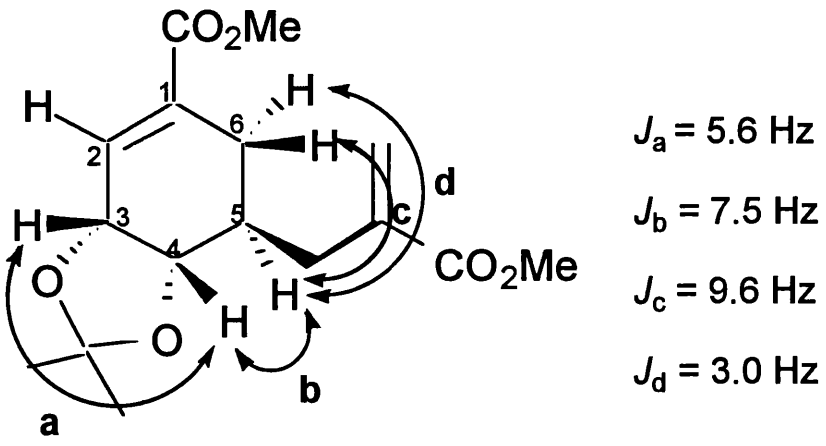


Figure 2.21

The coupling constants for **173** correlate reasonably well with the values calculated from the modified Karplus equation.[120] Even though this method needs to be used with caution, especially when electronegative groups are present, it seems

to be generally applicable to shikimic acid derivatives and analogues.[121] The geometry of the cyclohexene ring is essentially defined by the double bond, which forces the four carbon atoms C-6, C-1, C-2 and C-3 to be coplanar. The ring can then adopt either a half-chair or boat conformation, of which the former is generally favoured.[122]

Rapid conformational inversion is possible at room temperature and the observed conformation is a statistical average of all the conformations participating in the inversion cycle. However, the nature of the substituents determines which conformation is favoured energetically and, providing that the energy differences are significant, the observed conformation will approximate to the favoured species.

The resonance due to 4-H is especially informative in the spectra of shikimates. In this case a doublet of doublets was evident at δ= 4.03 p.p.m. ($J_{4,3}$ 5.6, $J_{4,5}$ 7.5 Hz). The relatively large 4,5 coupling is consistent with a half-chair conformation in which the chain at C-5 is in an pseudo-equatorial position and 4-H and 5-H are in a *trans* diaxial arrangement. The couplings between the 5-H and the 6α-H and 6β-H protons are consistent with this conformation.

The reaction between bromide **177** and allylstannane **178** was initiated with AIBN. The dissociation of AIBN in daylight yields two isobutyronitrile radicals with the consequent elimination of nitrogen (**fig. 2.22**).

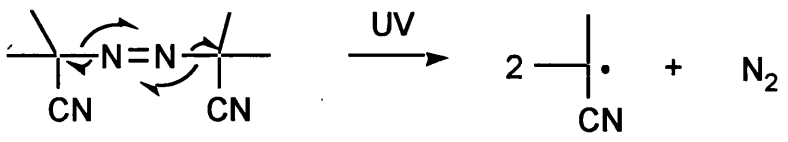
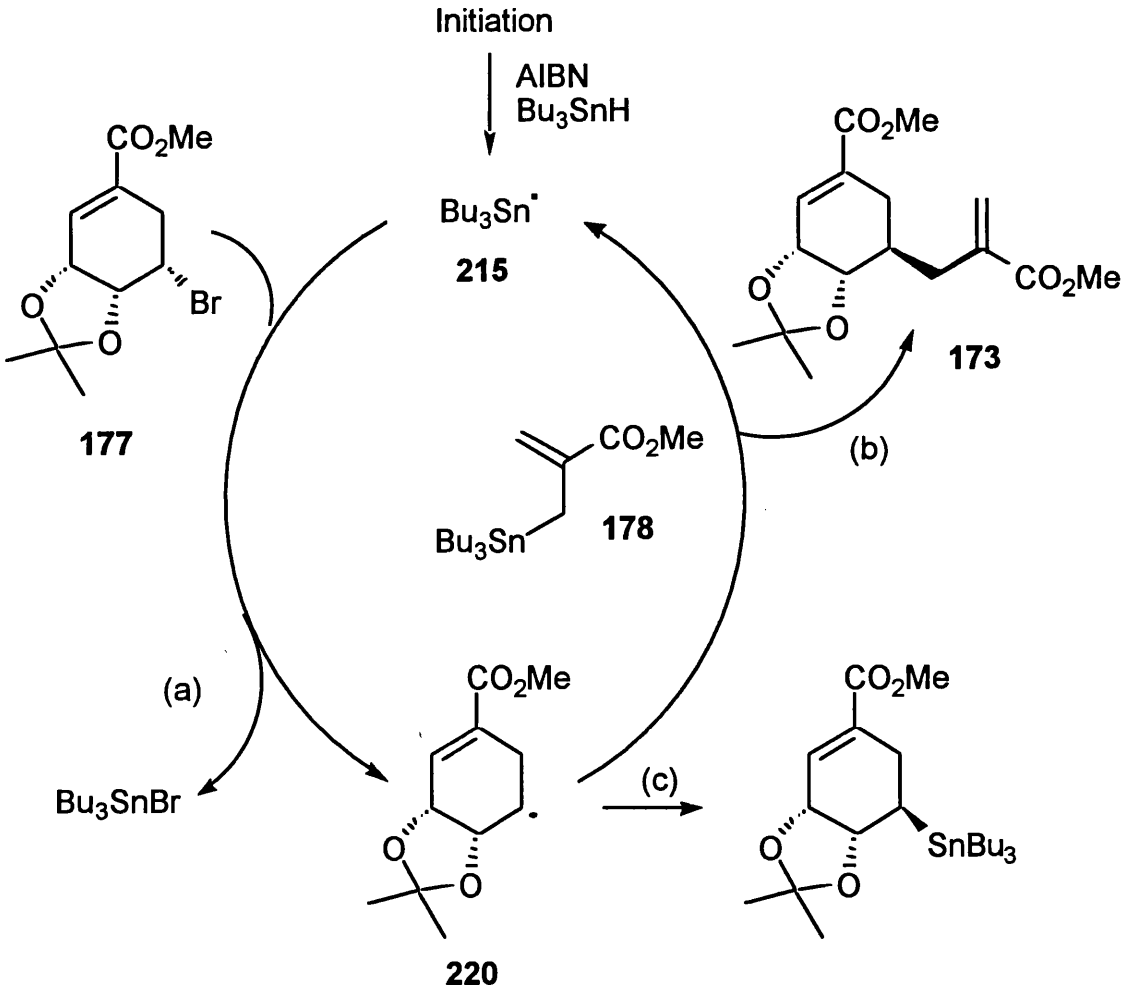


Figure 2.22

The initiation step of the reaction is the attack by an AIBN derived radical on the allylic tributyltin compound **178** in what essentially constitutes a SH' reaction, with the elimination of a tributyltin radical **215** (**scheme 2.23**). The tributyltin radical that is formed can then react with the bromine atom of **177** to yield a methyl

shikimate radical, which can then enter the 'radical cycle' by attacking another tributyltin molecule **178** in a SH' fashion to give the required carba analogue **173** and its stereoisomer **179**. The liberated tributyltin radical acts as a propagator in reaction with another molecule of bromide **177**. A recent review by Curran[123] detailed equivalent reaction conditions to those above, but suggested that only the β- stannyl radical **173** would be formed. The overall yield was similar to the combined yield of **173** and **179**. In our hands a 2.6:1 ratio of 5β:5α diastereoisomers was obtained. Interestingly Giese *et al.*[119] observed mainly attack at the equatorial position in their reaction (**scheme 2.19**). Dupuis, Giese *et al.* have shown that the intermediate free radical adopts the boat conformation **221** so as to maintain



Scheme 2.23

overlap between the higher energy SOMO of the alkoxyalkyl radical and the LUMO of the C-O bond of the adjacent 6-acetoxy group which would then have an axial disposition (**figure 2.24**).[124]

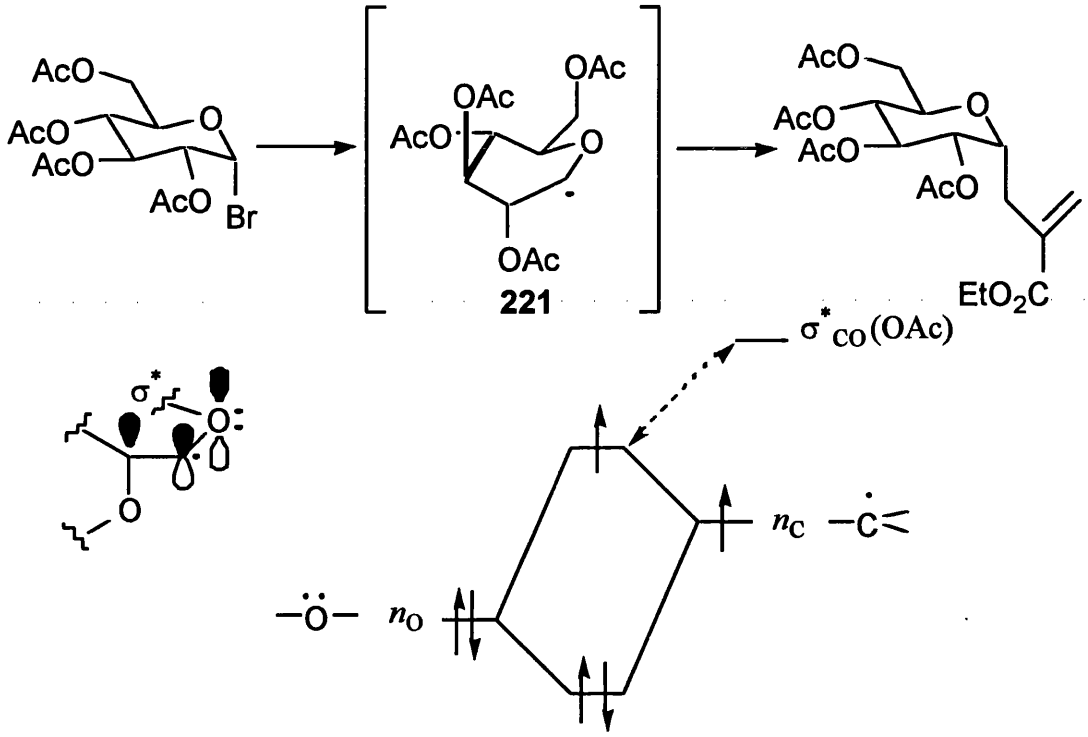


Figure 2.24

In most carbon-centred free radicals the unpaired electron occupies an orbital which has mainly p-character, so allowing attack from both sides.[124c] It is clear that on homolysis the stereointegrity at C-5 of **165** is lost, resulting in both the β and α radicals **220** and **222** (**figure 2.25**), but we thought that the attacking stannane **178** would then be subject to steric approach control (i) and give the β- product (**schemes 2.25, 2.26**). Furthermore the sidechain at C-5 is orientated pseudo-equatorially, the steric interaction with the acetonide protecting group is minimised, making **173** the lower energy stereoisomer. The relatively high yield of the alternative isomer **179** was unexpected.

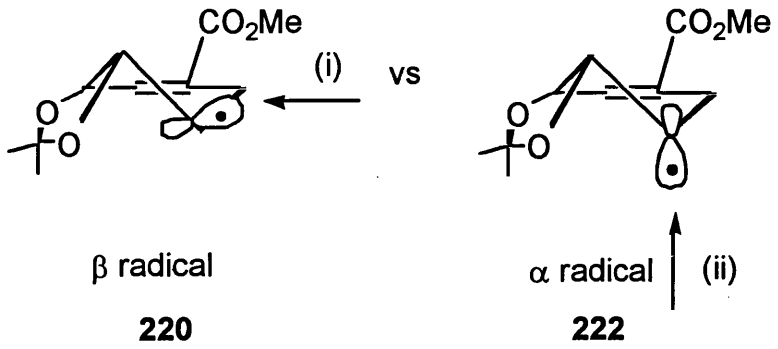
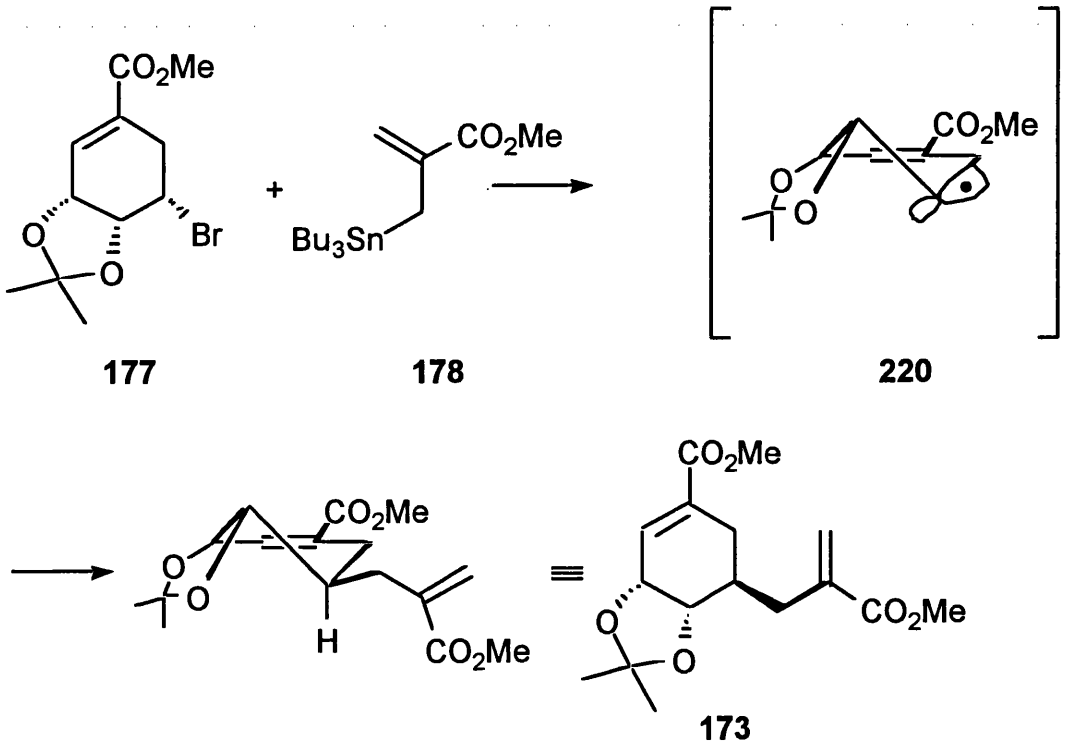


Figure 2.25



Scheme 2.26

Much work has been done on cyclohexyl radicals by Green *et al.* and Lefort *et al.* [125] and in the case of the 4-^{t}butylcyclohexyl species **223** (**figure 2.27**) there is a clear preference for attack at the axial position.[124] This is a result of reduced torsional strain, calculated by K. N. Houk *et al.*, in the developing transition state.[126] However, even with the stable conformation delivered by the tertiary butyl group, the reactions of the radical are sensitive to increasing 1,3-axial interactions or the size of

the reagent.[126] In our cyclohexene the ring is flattened out and it is conceivable that the constraints imposed in the cyclohexyl case are no longer applicable.

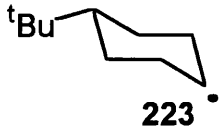


Figure 2.27

An explanation to account for this observation focuses on the lifetime of the radical **220** being longer than the time of the fragmentation step which forms the eventual products. It is possible that distortion of the stereochemistry at C-5 may have been allowed, thus enabling the approach of stannane **178** both equatorially and axially.

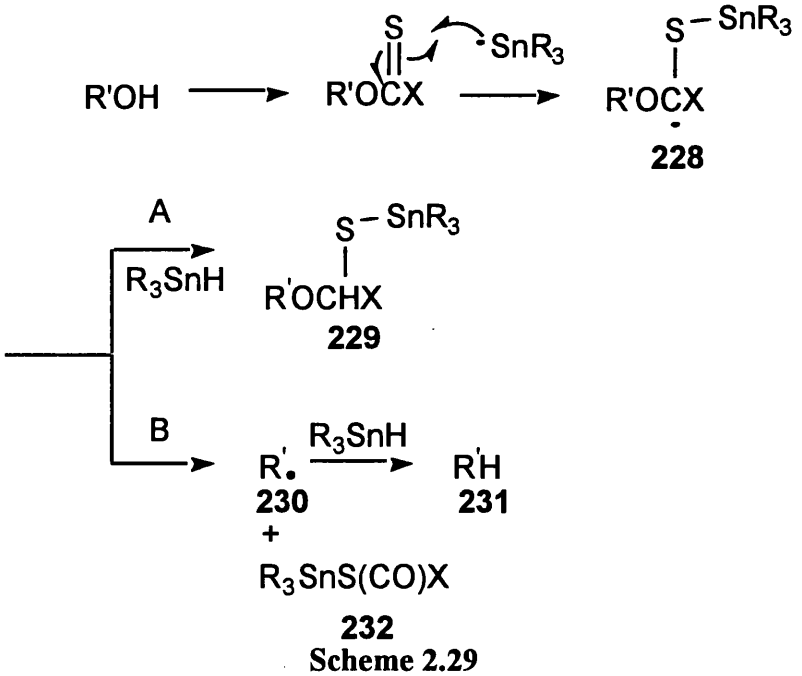
The reaction between 5α-bromide **177** and allylstannane **178** was then repeated but this time tertiary butyl peroxide was used as the radical initiator. The reaction was now complete in five hours and the ratio of 5β:5α was increased slightly to 2.65:1.

2.5 Thionocarbonates

With the conversion of the secondary alcohol **86** to a bromide being so low yielding we decided to synthesise analogues of **86** that had different radical leaving groups. Barton and McCombie have shown that thionocarbonyl derivatives of alcohols can be deoxygenated with tin halides.[127] O-Alkyl thiobenzoates **224**, O-phenyoxythiocarbonates **225**, S-methyl dithiocarbonates **226** and (alkoxy-(thiocarbonyl))imidazolides **227** (**figure 2.28**) are reduced to their deoxygenated compounds by tributyl tin hydride (**scheme 2.29**).[127,128]

Figure 2.28

In the first step the strong affinity of tin for sulfur leads to radical **228**. The formation of this radical is greatly favoured by the presence of a stabilising group X such as imidazolyl or S-methyl. Reaction paths A and B compete to lead to either the adduct **229** or to the formation of radical **230** and from there to product **231**. One possible driving force for the fragmentation of radical **230** (scheme B) is the formation of a new carbon-oxygen double bond **232**.[129]

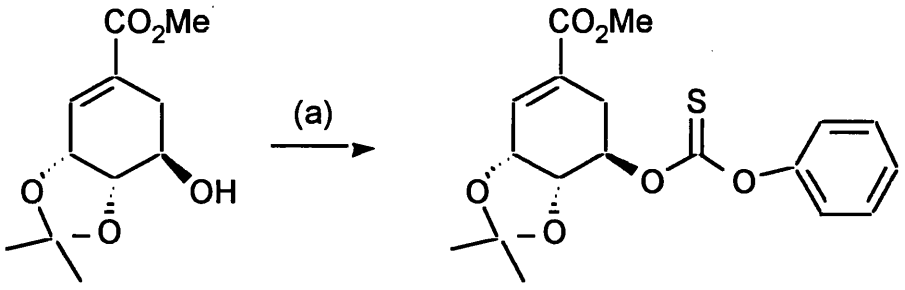


Scheme 2.29

We decided to synthesise a range of thiocarbonyl derivatives and react these with allyl stannane **178** in a bid to form the carba-analogue **173**.

2.5.1 Methyl 3α,4α-isopropylidenedioxy-5β-phenylthionoformate-cyclohex-1-ene-1-carboxylate

After consulting the review by Jasperse *et al.*,[116] the first derivative that we selected was the O-phenoxythionocarbonyl **233** (**scheme 2.30**). Alcohol **86** in dichloromethane was treated with pyridine and O-phenyl chlorothionoformate to afford thionocarbonate **233** as pale yellow crystals in 59% yield.

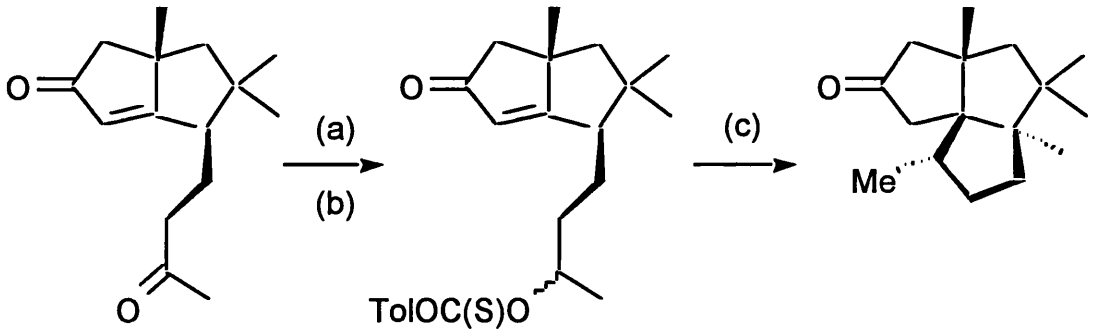


86 **233**

(a) O-phenylchlorothionoformate, py, DCM.

Scheme 2.30

Robins *et al.* [130] introduced the use of these derivatives as an improvement over other functional groups first recommended by Barton and McCombie.[128] Moreover there is a good precedent for our selection from the work by Nagarajan *et al.* in their synthesis of (±)- silphinene **235** (**scheme 2.31**).[131] Upon treatment with tin hydride, the *p*-tolyl thionocarbonate **234** cyclised to give **235** in 75% yield.

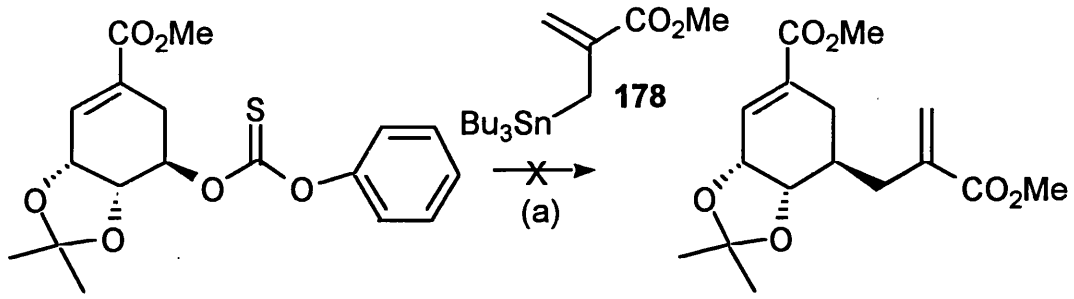


234 **235**

(a) $NaBH_4$; (b) TolOC(S)Cl; (c) Bu_3SnH, AIBN.

Scheme 2.31

In our hands the O-phenoxythionocarbonyl **233** was then reacted with allylstannane **178** to try and form compound **173** (**scheme 2.32**).



233 **173**

(a) AIBN, PhH, reflux.

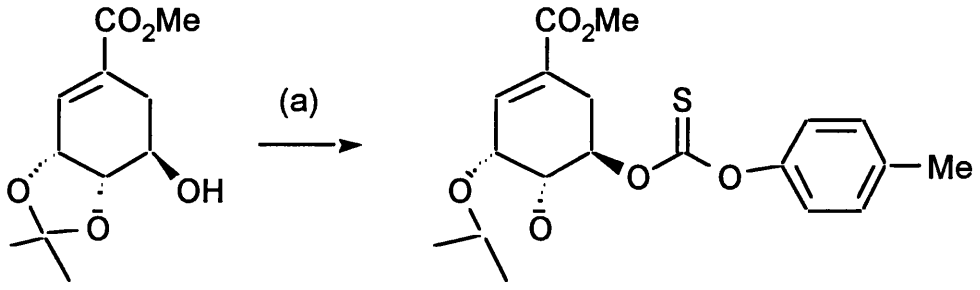
Scheme 2.32

Thionocarbonate **233** in toluene, was treated with two equivalents of allylstannane **178**, a catalytic amount (0.025 mmol) of AIBN was added and the reaction mixture was heated at 80°C for four hours. No product formed (t.l.c. monitoring), and we concluded that insufficient radical initiator had been added. Consequently another equivalent of AIBN was added and the reaction mixture was heated at 80°C for another fifteen hours. Still no product formed and so the temperature of the reaction was then raised to the boiling point of the solvent.

The reaction mixture was heated at reflux for five hours, but still no product was detected and the starting material was recovered. The reaction was repeated, but this time benzene was used as the solvent in place of the toluene used previously. Benzene was chosen in order to lower the risk of hydrogen abstraction from the solvent, but this procedure also failed.

2.5.2 Methyl 3α,4α-isopropylidenedioxy-5β-*p*-tolylthionoformate-cyclohex-1-ene-1-carboxylate

As we were unable to initiate the radical cleavage of **233**, we decided to synthesise the O-*p*-tolylthionocarbonate **236** (**scheme 2.33**). Alcohol **86** in dichloromethane was treated with pyridine and O-p-tolylchlorothionoformate[132] to afford O-*p*-tolylthionocarbonate **236** as pale yellow crystals in 85% yield.



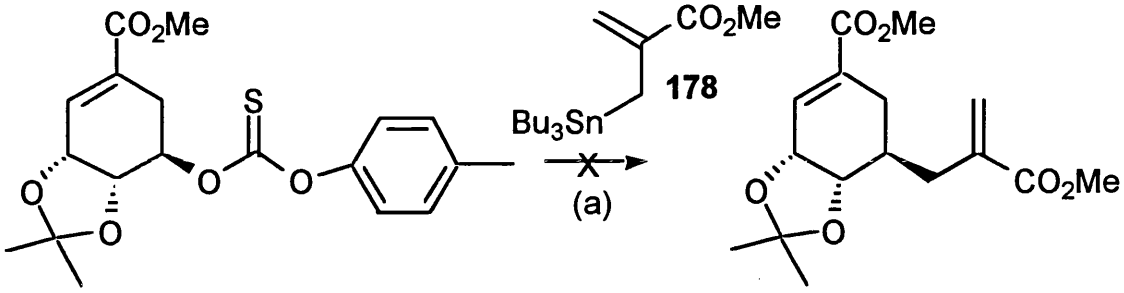
86 **236**

(a) O-*p*-tolylchlorothionoformate, py, DCM.

Scheme 2.33

The thionocarbonate **236** was dissolved in benzene and treated with two equivalents of allylstannane **178** plus a catalytic amount of AIBN and the mixture was heated at reflux for twenty hours (**scheme 2.34**). Again no product formed. The

reaction was repeated using toluene as the solvent in the hope that the increase in temperature would increase the rate of the reaction, but after fifteen hours no product formed.



(a) AIBN, PhH, reflux.

Scheme 2.34

A different method of radical initiation for the reaction between the thionocompounds **233** and **236** and allylstannane **178** was then sought. We decided to repeat the reactions with tertiary butylperoxide, the same initiator that had increased the yield of the reaction between tributyl tin hydride and tosylate **209** (**scheme 2.14**). However this change failed to lead to a coupling reaction. Azobiscyclohexylnitrile (ACN) has been used to good effect as a radical initiator[133] by Keck *et al.* in their synthesis of PGF2α.[134] These workers found that in their work radical initiation by AIBN was slow and low yielding, even when solutions of the initiator in benzene had been added slowly to the reaction mixture. By using ACN in toluene at reflux however, the yield of the reaction was almost doubled (72% as compared to 43% for AIBN). We repeated our reaction of thionocarbonyls **233** and **236** with allylstannane **178** and this time we used 0.1 equivalents of ACN as our initiator. The reaction mixture was heated to reflux in toluene for nine hours but yet again no reaction occurred.

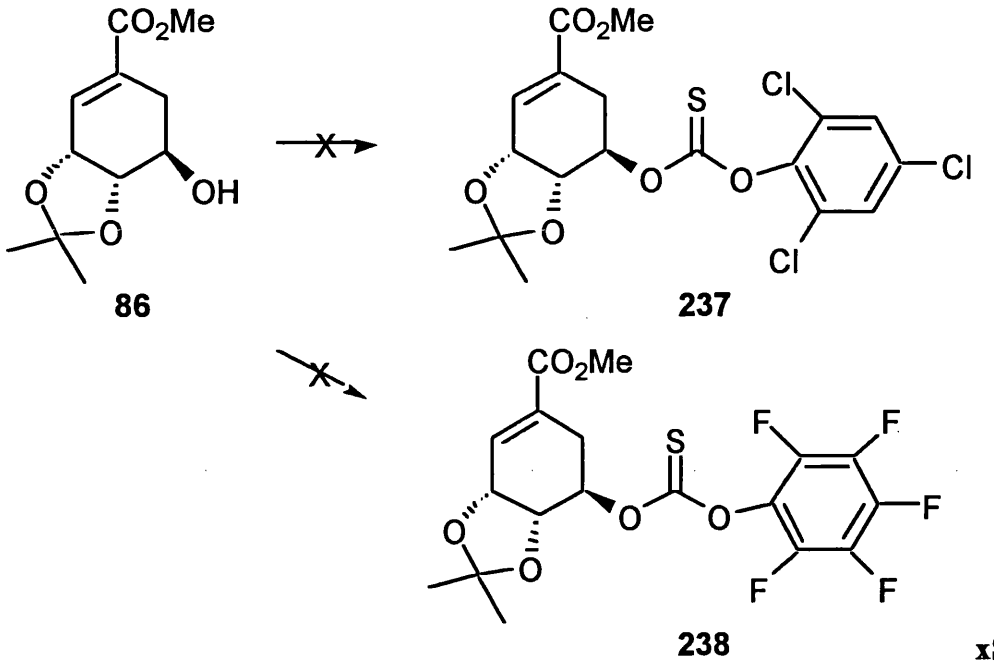
A search of the literature showed that photoirradiation with ultra-violet light is often sufficient to initiate the reactions of thionocarbonyl compounds with tributyl tin

hydride. Such reactions are achieved using Hanovia medium-pressure mercury lamps equipped with pyrex filters to remove the low wavelength light ($\lambda < 300$ nm).[131] O-*p*-Tolylthionocarbonate **236** in benzene was exposed to a 400W medium-pressure mercury lamp. After four hours reaction time most of the starting material had reacted to produce at least twenty different close running spots by t.l.c., but none of these spots co-incided with those attributable to the desired products **173** and **179**. The reaction was continued for another three hours and even more compounds were formed but not all the starting material had been used. The reaction mixture was subjected to column chromatography in an attempt to isolate and characterise some of the products. Unfortunately no pure compounds could be obtained even after repeated chromatography. The best we could achieve were samples containing about five products that ran together on t.l.c. (the difference in R_F was only 0.1). ^{1}H n.m.r. data obtained from these fractions did not appear to show the presence of any alkenic compounds. For example, the distinctive peaks at $\delta = 5.68$ ppm and $\delta = 6.29$ ppm that arise from the resonances of the two protons at C-1' of compound **173** were missing. The reaction was repeated but this time thionocarbonate **233** was used instead of **236**. As before a multitude of products were formed, none of which co-incided with the desired products.

2.5.3 Methyl 3α,4α-isopropylidenedioxy-5β-trichlorophenylthiono-formate-cyclohex-1-ene-1-carboxylate

Barton *et al.* have recently introduced a new series of thionocarbonates to improve the radical deoxygenation of secondary alcohols.[135] These increase the radicophilicity of the thione group by the incorporation of electron withdrawing groups on an attached phenyl group.

We attempted to synthesise the trichlorophenyl **237** and pentafluorophenol **238** derivatives to see if these would react with allylstannane **178** (**scheme 2.35**).



xScheme 2.35

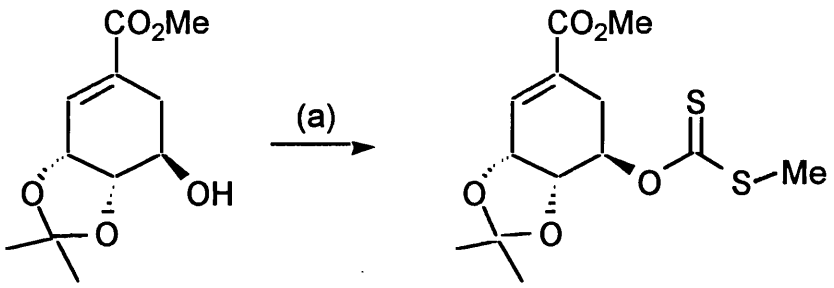
We first tried to synthesise the trichlorophenyl derivative **237**. A solution of alcohol **86** in dichloromethane was treated with triethylamine and the reaction mixture stirred under an atmosphere of nitrogen. O-2,4,6-Trichlorophenylchlorothiono-formate was added dropwise and the reaction was stirred at room temperature for two hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present. The solvent was removed under reduced pressure and toluene was added along with a catalytic amount of N-hydroxysuccinimide and the reaction was heated at 80°C for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

2.5.4 Methyl 3-α,4α-isopropylidenedioxy-5β-pentafluorophenyl-thiono-formate-cyclohex-1-ene-1-carboxylate

We then tried to synthesise the pentafluoro derivative **238**. A solution of alcohol **86** in toluene was treated with N-hydroxysuccinimide and the reaction mixture stirred under an atmosphere of nitrogen. Pyridine and pentafluorophenylchlorothionoformate were then added in sequence and the reaction mixture was heated at 80°C for 6 hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion, with only starting material (**86**, R_F = 0.51) remaining present.

2.5.5 Methyl 3α,4α-isopropylidenedioxy-5β-S-methyldithio-carbonyl-cyclohex-1-ene-1-carboxylate 239

Unfortunately as we were unable to synthesise either of **237** or **238** we decided to prepare the xanthate **239** (**scheme 2.36**). A solution of alcohol **86** in THF was treated with a solution of sodium hydride and imidazole in THF. The reaction mixture was stirred under an atmosphere of nitrogen for two hours and was then treated with carbon disulfide dropwise over fifteen minutes. Methyl iodide was then added dropwise over fifteen minutes and the reaction mixture stirred for a further thirty minutes to afford xanthate **239** as colourless prisms in 64% yield.

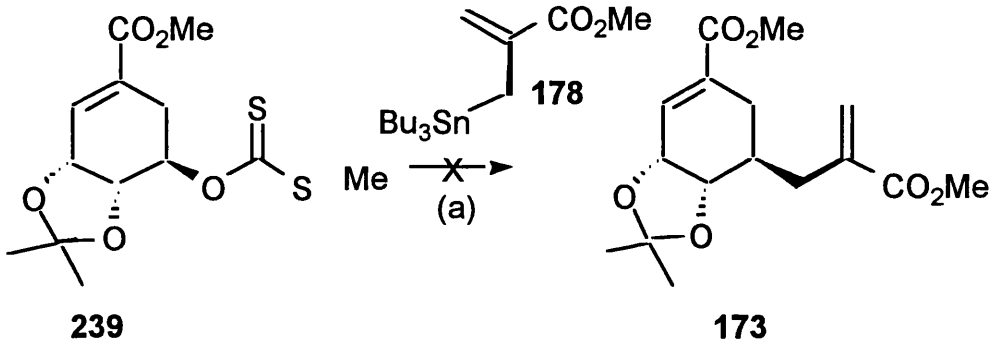


86 **239**

(a) NaH, Imidazole, THF, CS_2, MeI.

Scheme 2.36

Xanthate **239** was then treated with two equivalents of allylstannane **178** (**scheme 2.37**) and a catalytic amount of ACN, in boiling toluene, to try and form **173**. Unfortunately none of the desired product was obtained.



239 **173**

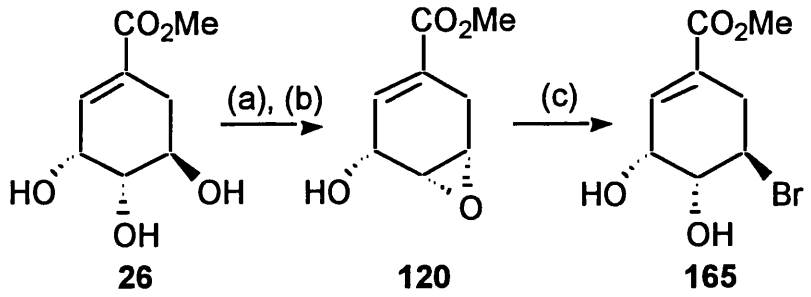
(a) ACN, PhMe, reflux.

Scheme 2.37

At this stage because the radical reactions between thionocarbonates **235**, **236** and **239** and allylstannane **178** had been unsuccessful we decided to return to our original plan of synthesising 5-bromo shikimates.

2.6 Synthesis of 5β-bromoshikimate 165

We needed to synthesise further supplies of methyl 5-bromoshikimate and we were attracted by a paper by Knowles and Anderson,[86] who synthesised 5β-bromoshikimate **165** from methyl shikimate **26** via Berchtold's epoxide[59] **120** (**scheme 2.38**). The epoxide was formed from methyl shikimate by the Mitsunobu reaction[136] and then ring opened regioselectively by treatment with Li_2NiBr_4 .[137]



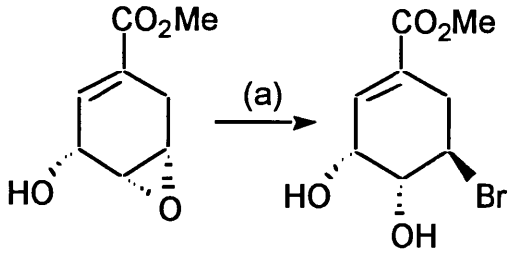
26 **120** **165**

(a) Ph_3P, DEAD, THF; (b) 120^0C, 0.5 mmHg; (c) Li_2NiBr_4, THF.

Scheme 2.38

2.6.1 Epoxide Formation - The Mitsunobu Reaction

We decided to follow a similar route to synthesise bromide **165** (**scheme 2.39**) but to open the epoxide with lithium bromide and acetic acid. (-)-Methyl shikimate **26**, in THF, was cooled to 0^oC and was treated with two equivalents of triphenyl phosphine and two equivalents of freshly distilled DEAD. This gave the epoxide **120** in 27% yield as a pale yellow oil, which crystallised on standing as long colourless needles.



120 **165**

(a) LiBr, AcOH, THF.

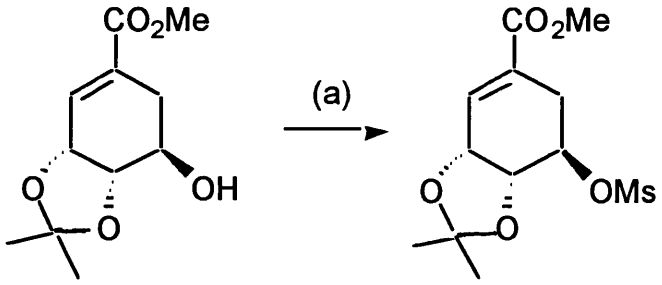
Scheme 2.39

The reason for the low yield of the reaction was the problem in removing the triphenylphosphine oxide that is generated in the reaction. Following the procedure by Berchtold *et al.*,[59] we decided to distil the reaction mixture prior to chromatography. Thus the solvent was removed from the reaction mixture under reduced pressure and the residue was then distilled using a Kugelrohr apparatus. Material distilling up to 130°C at a pressure of 0.5mm was collected and this was diluted with diethyl ether, which caused N,N'-bis(ethoxycarbonyl)hydrazine to precipitate, The solvent was removed from the filtrate to afford epoxide **120** in 35% yield after chromatography. This was an improvement on the previous synthesis but was still not as good as we had hoped.

2.6.2 Methyl 3α,4α-isopropylidenedioxy-5β-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate

Another route to epoxide **120** was then sought. We decided to convert the free hydroxyl group of **86** to a good leaving group i.e. triflate or mesylate. After deprotection of the acetonide we envisaged that the leaving group of the product could then be displaced to give the epoxide **120**.

The mesylate derivative **240** was obtained by treatment of **86** with methanesulfonyl chloride and pyridine in dichloromethane at 0°C (**scheme 2.40**).



86 **240**

(a) (method 1) py, MsCl, DCM, 0^0C - R.T., 68%;
(method2) py, MsCl, 0^0C - R.T., 80%;
(method3) Et_3N, DCM, THF, 0^0C - R.T., 98%

Scheme 2.40

After the addition of methanesufonyl chloride the reaction was allowed to warm to room temperature. After seventy one hours the mesylate **240** was produced in 68% yield as a clear colourless oil, that was crystallised from chloroform. By reacting methyl shikimate **86** in pyridine in the absence of dichloromethane the reaction was complete in only seventeen hours and in 80% yield. Removal of the pyridinium chloride generated in the reaction was a problem as it has an almost identical R_F to that of the product. In order to simplify the work-up triethylamine was used instead of pyridine. This gave a bright yellow precipitate immediately on the addition of the methanesufonyl chloride, and the reaction was complete in only fifteen minutes giving a yield of **240** of 98%.

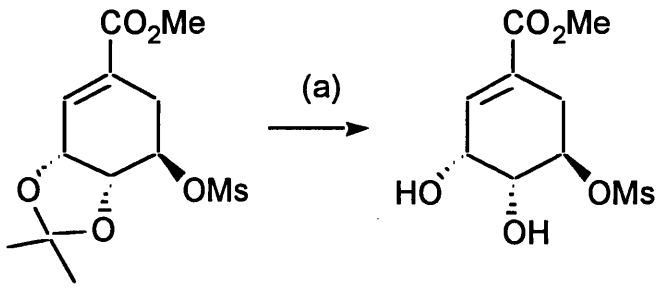
The triethylammonium chloride is easy to remove from the reaction mixture and any which remains in the crude product can be easily separated by column chromatography (**table 2.41**).

Reagents	% yield of 240
py, MsCl, DCM	68
Py, MsCl	80
Et_3N, MsCl, THF, DCM	98

Table 2.41

2.6.3 Methyl 3α,4α-dihydroxy-5β-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate

The next step involved the removal of the acetonide protecting group (**scheme 2.42**). We decided to use the method that has been demonstrated to work well in the shikimate series of compounds.[35,103] A solution of protected mesylate **240** in tetrahydrofuran was treated with aqueous acetic acid. This was heated to 60°C for thirty five hours to afford mesylate **241** in 79% yield.



240 **241**

(a) (method1) AcOH, THF, H_2O,60°C, 3 h, 79%;
(method2) 1N HCl, THF, 55°C, 2.5h, 52%;
(method3) 1N HCl, THF, 5h, 81%.

Scheme 2.42

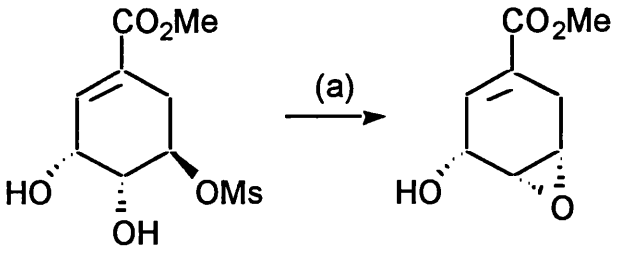
Keck *et al.*[138] recently reported a quick method for the removal of acetonides. This gives high yields and uses aqueous hydrochloric acid in tetrahydrofuran. In an effort to speed up the removal of the acetonide from **240** we decided to follow this procedure. To a solution of mesylate **240** in tetrahydrofuran was added a 1M solution of hydrochloric acid. This was heated to 50°C for two and half hours to afford the unprotected mesylate **241**, but in only 52% yield. Fortunately when a solution of **240** in THF was treated with 1M HCl and stirred at room temperature the reaction was complete after five hours and afforded the product in 81% yield (**table 2.43**).

Reagents	% yield of 241
AcOH, H_2O, THF, 60°C	79
1M HCl, THF, 55°C	52
1M HCl, THF	81

Table 2.43

2.6.4 Methyl *cis*-3-hydroxy-4,5-oxycyclohex-1-ene-1-carboxylate

The final step in our renewed synthesis of epoxide **120** involved the elimination of the mesylate functionality from **241** (**scheme 2.44**).[138] A solution of the mesylate **241** in tetrahydrofuran, was treated with a slight excess (1.1 equiv.) of potassium tertiary butoxide. After three hours this afforded the epoxide **120** as a colourless oil, which rapidly crystallised as white needles in 43% yield.



241 **120**

(a) KO^{t}Bu, THF.

Scheme 2.44

When a solution of **241** in THF was treated with potassium tertiary butoxide at 0°C the yield was increased up to 51%. By cooling the reaction mixture to -78°C before the addition of the potassium tertiary butoxide the yield increased still further to 95% (**table 2.45**).

Reagents	%yield of 120
KO^{t}Bu, THF	43
KO^{t}BU, THF, 0°C	52
KO^{t}Bu, THF, -78°C	95

Table 2.45

A comparison of the ^{1}H n.m.r of the epoxide **120** formed from methyl shikimate with that formed *via* the mesylate **241** showed them to be identical. Our route produced epoxide **120** from (-)-methyl shikimate **26** in an overall yield of 74%. This compares favourably with the 35% yield of epoxide **120** we obtained by the Mitsunobu route[136] as used by Berchtold *et al.*[59] (**section 2.6.1**).

2.6.5 Halohydrin Formation

The next step involved the ring opening of the epoxide to give either the bromo or iodo halohydrin **165** or **242**. The regiospecific opening of epoxides to give halohydrins has generated considerable interest. Methods based upon hydrogen halides are not considered appropriate because they often lead to the formation of reaction byproducts. The opening of unsymmetrically substituted epoxides with Br_2/PPh_3, BBr_3, Me_2BBr_6, $(Me_2N)_2BBr$, Me_3SiBr, pyr.HCl or $BF_3.Et_2O/n\text{-}Bu_4NI$ suffers from moderate regioselectivity and/or the propensity to react with a range of nucleophilic functional groups. More recently dilithium tetrabromonickelate (Li_2NiBr_4) was reported to be a source of "soft" nucleophilic bromide, which regioselectively converts epoxides to halohydrins under mild conditions. Many of the above methods require the *in situ* preparation of the reagents, and no single procedure is suitable for the preparation of both bromo and iodo halohydrins.

A method to open the epoxide in a regiospecific fashion which has none of the above problems was sought. We decided to use the approach devised by Bajwa and Anderson.[139] They used lithium halides, in the presence of acetic acid, to convert epoxides regioselectively to halohydrins under mild conditions, even when sensitive functional groups were present. By changing the lithium salt it is possible to generate either the iodo- of bromohydrin, so giving easy access to the 5-iodo compound **242** as well as the bromo compound **165**.

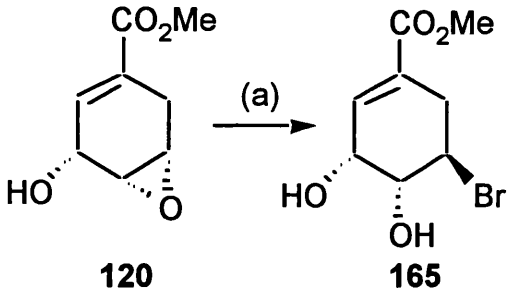
We decided to synthesise the iodocompound **242** as iodo compounds are known to more readily undergo radical elimination reactions with stannanes. The transferability of various atoms and groups X (**figure 2.46**) to tin radicals is generally in the order I > Br > SePh ≈OC(S)SMe > Cl > SPh.[140] The reactivity of various radicals R. toward tin hydride is aryl ≈ vinyl > alkyl > allyl ≈ benzyl.

Primary, secondary, and tertiary alkyl radicals show very little difference in their reactivity toward tin hydride.

Figure 2.46

A solution of epoxide **120** in THF was treated with acetic acid and lithium bromide to give bromide **165** in 78% yield **(scheme 2.47)**.

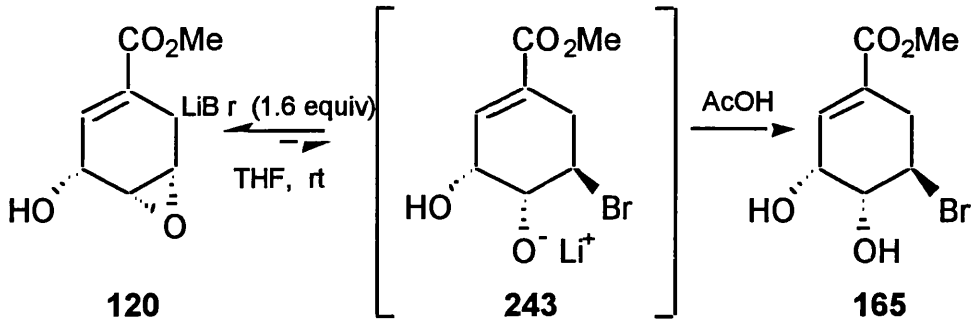
The proposed mechanism for the reaction involves reversible epoxide ring opening by attack by a bromide ion. The reaction is then driven to completion by protonation of the intermediate alkoxide **243** by acetic acid to give halohydrin **165** **(scheme 2.48)**. The acetic acid also reduces the basicity of the halide ions which in some cases can lead to side products.



120 **165**

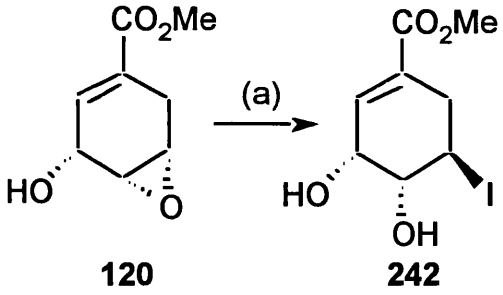
(a) LiBr, AcOH, THF.

Scheme 2.47



Scheme 2.48

The 5-β- iodo compound **242** was formed in a similar way to that of bromo **165**. A solution of epoxide **120** in THF was treated with acetic acid and lithium iodide to give iodide **243** in 85% yield (**scheme 2.49**). Care was taken to exclude light from the reaction due to the weakness of the C-I bond, as we did not want any side reactions to complicate the outcome of the process.



(a) LiI, AcOH, THF.

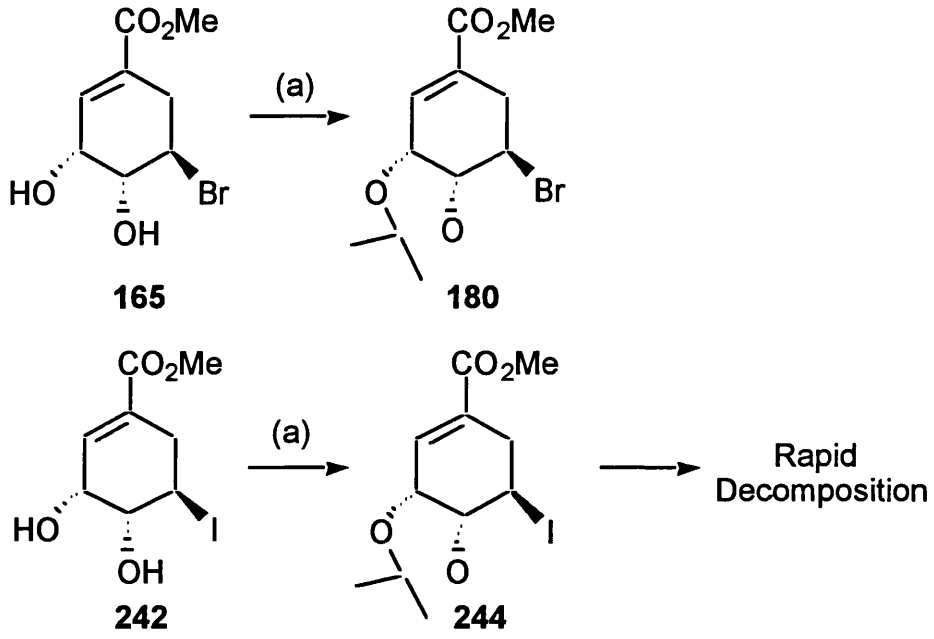
Scheme 2.49

2.6.6 Protection of Halohydrins

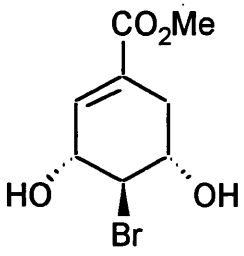
To prove the regiochemistry of the bromide **165** and the iodide **242** the suspected 2,3-*cis* diol functionalities were protected as their respective acetonides, **180** and **244** (**scheme 2.50**). This was done in the same way as the protection of methyl shikimate **26** (**section 2.2.1**).

The formation of the acetonide indicated that the epoxide **120** had indeed been regioselectively opened by lithium bromide to yield the bromide **165** and not the bromide **245**.

The H-4,H-5 coupling for **165** is consistent with a half-chair conformation in which the bromide at C-5 is in an equatorial position and 4-H and 5-H are in a *trans* diaxial arrangement. The couplings between the 5-H and the 6α-H and 6β-H protons are consistent with this conformation.



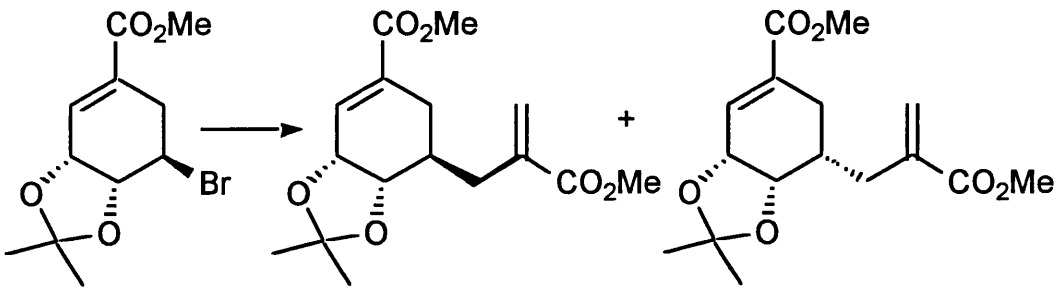
Scheme 2.50



245

2.7 Coupling Reactions to Afford Methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonylprop-1-en-3-yl] -cyclo-hex-1-ene-1-carboxylate 173 and Methyl 3α,4α-isopropylidenedioxy-5α-[2-methoxycarbonylprop-1-en-3-yl] -cyclo-hex-1-ene-1-carboxylate 179

A solution of bromide **180**, in degassed toluene, was treated with two equivalents of the allylstannane **178** and a catalytic amount of AIBN to afford the carba analogues of protected 5-enolpyruvylshikimate **173** and **179** in an overall yield of 46% (**scheme 2.51**). A 2.7:1 ratio of 5β:5α diastereoisomers was obtained which is in contrast to the radical coupling reaction between **180** and **178** where only a 2.6:1 ratio was observed.



180 **173** **179**

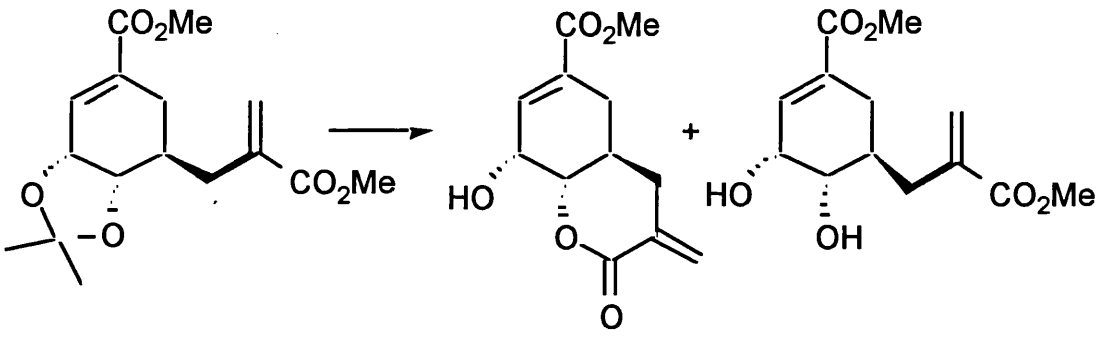
Scheme 2.51

When ACN was used as the radical initiator instead of AIBN the reaction was complete in only two hours in an overall yield of 62%. This time the ratio of 5β -carba chain (**173**) to 5α -carba chain (**179**) was 3.35:1. This increase in the desired 5β diastereoisomer **173** is obviously due to the decreased reaction time.

Now that we had managed to assemble the carbon skeleton which we had targeted, in a reasonable yield from shikimic acid **1** (27%), the remaining steps in the synthetic sequence to the desired 5β -methylene lactone **175** were simple deprotection steps.

2.8 Acetonide Deprotection

The acetonide protecting group was removed by treatment of **173** with mild acetic acid (2:1:1 acetic acid / water / tetrahydrofuran) to form the corresponding diol **246** in 38% yield (**scheme 2.52**). In the course of the reaction, it was found by t.l.c. monitoring that two products were present in the reaction mixture. Their R_Fs in hexane - ethyl acetate (1:3) were 0.49 and 0.40, suggesting that they were of a similar polarity. Once the products had been isolated by column chromatography, ^1H n.m.r. data showed them to be the desired lactone **175** and the diol **246** respectively.



173 **175** **246**

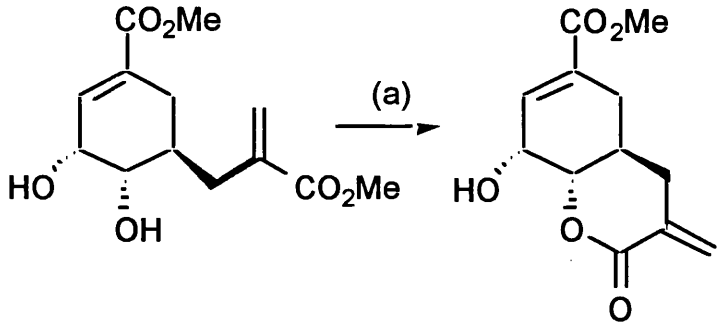
Scheme 2.54

This result was surprising since Ganem *et al.* and Bartlett *et al.* reported no evidence of any lactone formation in similar reactions with the enolpyruvyl equivalents of our compounds (**section 1.3.2, scheme 1.29** and **scheme 1.30**).[61,62] Both Ganem and Bartlett deprotection reactions were performed over a much shorter time scale than ours, and so it was thought that the deprotection and cyclisation were time dependent. The reaction was then repeated, but even with increased reaction times the relative ratio of diol to lactone could not be increased in favour of the lactone. Although not all of **173** could be converted to the lactone **175** via this one reaction, the result was nevertheless synthetically useful as the remaining diol **246** could be cyclised to give the desired lactone **175** by following either the work undertaken by Ganem[61] or Bartlett[62] (**section 1.3.2** , **scheme 1.29** and **scheme 1.30**).

2.9 Formation of *Trans*-8α-Hydroxy-6-methoxycarbonyl-3-methylene-4a,5,8,8a-tetrahydro-4H-benzo[e]pyran-2-one 175

Ganem *et al.*[61] reported a three stage deprotection sequence from the enolpyruvly diol diester through to the corresponding lactone via the associated enolpyruvyl diol acid. The acetonide was removed by using aqueous acetic acid, the resulting diol was then treated with aqueous base to give the mono ester which when treated with DCC / DMAP cyclised to give lactone **103** (**scheme 1.29**). Bartlett[62] reported a direct method of cyclisation from the diol by using potassium carbonate (**scheme 1.30**). This method precludes the necessity of activating the side chain carbonyl group for ring closure as described by Ganem.

Treatment of our diol diester **246** with potassium carbonate in acetonitrile at 50°C afforded lactone **175** in 63% yield (**scheme 2.53**).



246 **175**

(a) K_2CO_3.

Scheme 2.53

Lactone **175** shows distinctive peaks at δ = 5.66 ppm and δ = 6.48 ppm that arise from the resonances of the two protons at C-1'. For lactone **175** a doublet of doublets was evident at δ = 4.23 p.p.m. ($J_{4,3}$ 3.0, $J_{4,5}$ 10.5 Hz, 4-H). The relatively large 4,5 coupling is consistent with a half-chair conformation in which the chain at C-5 is in an equatorial position and 4-H and 5-H are in a *trans* diaxial arrangement.

The couplings between the 5-H and the 6α-H and 6β-H protons are consistent with this conformation (**figure 2.54**).

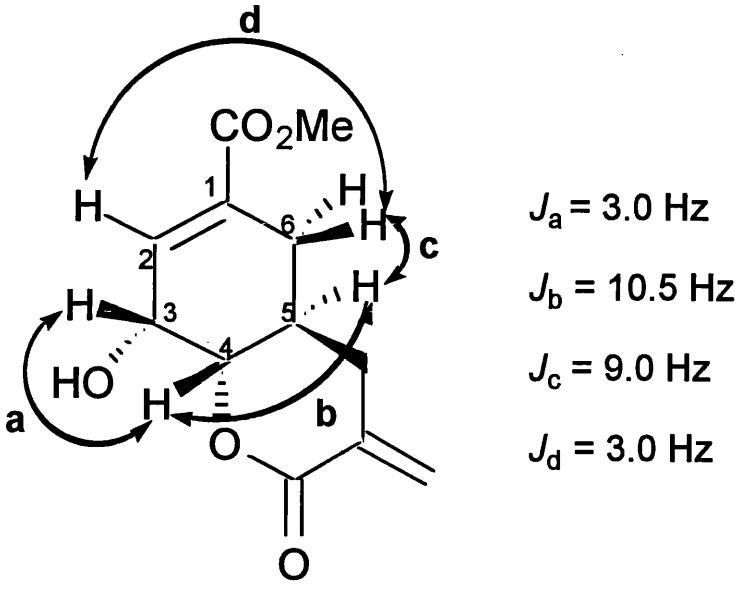
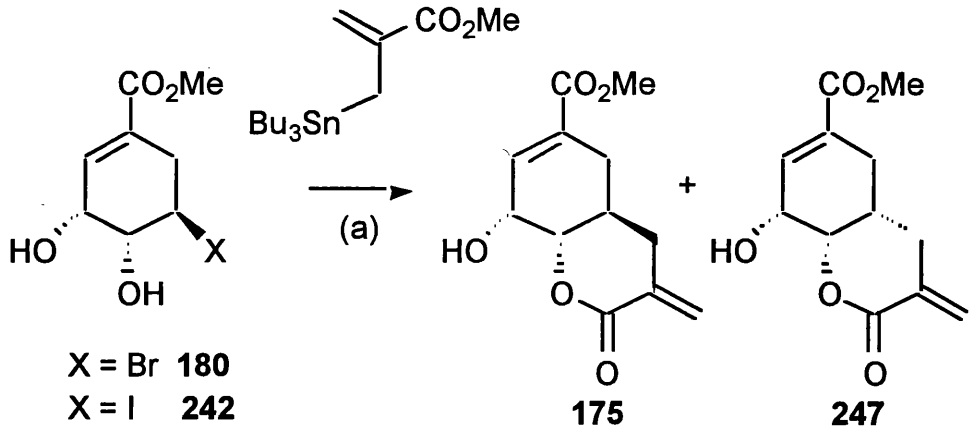


Figure 2.54

2.10 Coupling Reactions to Afford *Trans*-8α-Hydroxy-6-methoxy-carbonyl-3-methylene-4a,5,8,8a-tetrahydro-4H-benzo[e]pyran-2-one (175)

A more direct route to lactone **175** is possible by coupling bromide **180** or iodide **242** with allylstannane **178** (**scheme 2.55**).



(a) ACN, PhMe, reflux.

Scheme 2.55

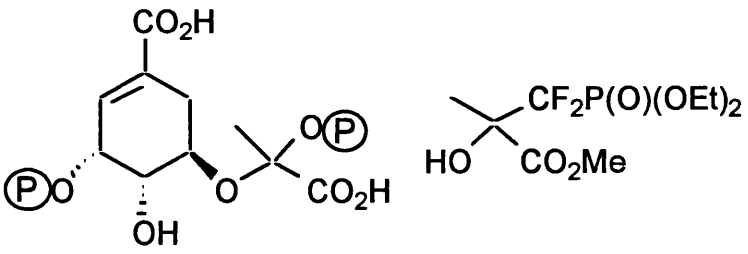
A solution of bromide **180** in toluene was treated with allylstannane **178** and a catalytic amount of ACN. Boiling the reaction mixture for three hours afforded 5-β-lactone **175** in 51% yield along with 5-α-lactone **247** in 19% yield. When we replaced bromide **180** with iodide **242** and repeated the reaction lactone **175** was formed in 56% yield after only two hours, with lactone **247** being formed in 23% yield.

Lactone **247** shows distinctive peaks at $\delta = 5.65$ ppm and $\delta = 6.53$ ppm that arise from the resonances of the two protons at C-1'.

2.11 Further Epoxide Opening Reactions

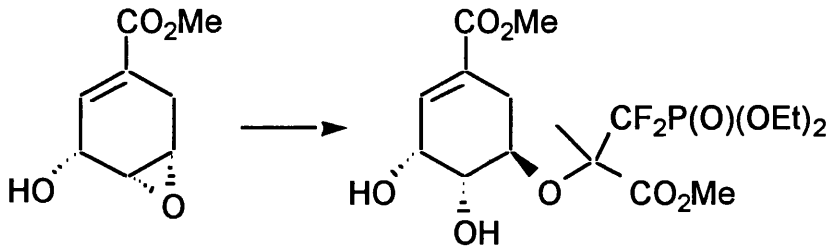
2.11.1 Attempted Synthesis of an Analogue of Tetrahedral Intermediate 12

Tetrahedral intermediate **12** is an unstable compound that is involved in the 5-EPS-3-P reaction. Stable analogues of this high energy intermediate would be expected to benefit from the extra binding affinity that these species experience.[84]



12 **248**

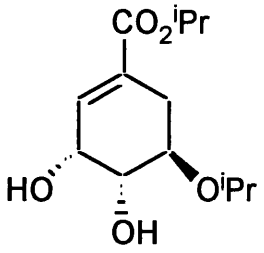
Compound **248** has recently been synthesised in the Bath Laboratory[141] and so we decided to try and open epoxide **120** with **248** to generate analogue **249** (**scheme 2.56**).



120 **249**

Scheme 2.56

Sharpless *et al.* have used titanium isopropoxide to open epoxides with a variety of nucleophiles.[142] Following this procedure, a solution of epoxide **120** in benzene was treated with methyl [3,3-difluoro-3-(diethoxyphosphinyl)-2-hydroxy-2-methyl]propionate **248** and one equivalent of titanium isopropoxide. The reaction mixture was then boiled for four hours but t.l.c. indicated that no reaction had occurred. The reaction was repeated but this time 2 equivalents of titanium isopropoxide was used. After stirring at room temperature for three hours a new product spot was visible by t.l.c. The new product was isopropyl 3α,4α-hydroxy-5β-isopropylcyclohex-1-ene-1-carboxylate **250**. There is some precedence for the opening of epoxides by isopropyl alcohol formed from titanium isopropoxide.[143]



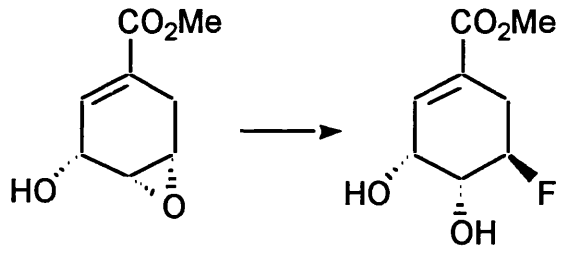
250

2.11.2 Fluorohydrin Formation

As the titanium isopropoxide($Ti(O^iPr)_4$) had opened the epoxide instead of fluorocompound **248** we decided to use another Lewis acid. The reaction was repeated but this time $BF_3.Et_2O$[144] was used instead of the $Ti(O^iPr)_4$.

Unfortunately, this time epoxide **120** was opened with fluorine to give **251** in 8% yield (**scheme 2.57**). Takaishi *et al.* have reported the opening of tricyclic epoxides with $BF_3.Et_2O$ to form fluorohydrins.[145]

To confirm the structure of **251**, epoxide **120** was treated with HF.py[146] and fluorohydrin **251** was formed in 43% yield.



120 **251**

Scheme 2.57

A shortage of time meant that further investigations into the opening of epoxide **120** with **248** could not be undertaken.

EXPERIMENTAL

Solvents and reagents

All solvents were distilled and dried before use. Petrol refers to petroleum ether boiling in the range 60-80°C. Tetrahydrofuran (THF) was pre-dried over sodium wire and then heated to reflux over sodium benzophenone ketyl under an atmosphere of nitrogen until anhydrous. This was redistilled prior to use. All other solvents and reagents were purified using the procedures described in *Purification of Laboratory Chemicals.*[147]

Chromatography

Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide during reactions and for assessing purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator were used and were visualised using ultra violet light wavelength 254nm where possible. Plates were developed by treatment with a 0.5% (w/v) aqueous solution of potassium permanganate, followed by warming of the plate.

Medium pressure flash columns were routinely run using Amicon Matrex 60Å silica gel. Flash chromatography was performed under medium pressure using a small hand bellow. Columns were packed as a slurry, the material to be chromatographed introduced as either a solution in the eluting solvent, a solution in DCM or preabsorbed on to silica and then applied as a thin layer to the top of the column.

Spectroscopy

The multiplicities of the resonances are denoted as follows: s (singlet), d (doublet), t (triplet), q(quartet) and m(multiplet)(br denotes a broad peak).

Melting points (m.p.) were determined on Electrothermal Mk III apparatus and are uncorrected.

Elemental micro-analyses were carried out using a Carlo-Erba 1106 Elemental Analyser.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 spectrophotometer and peaks are reported in wavenumbers (cm^{-1}). Samples were prepared as nujol mulls unless otherwise stated.

^{1}H and ^{13}C nuclear magnetic resonance (n.m.r.) spectra were recorded on a Jeol GX270 (270MHz) spectrometer or on a Jeol GX400 (400MHz) spectrometer where stated. For ^{13}C, operating frequency was 67.8 MHz, using 90 and 135 DEPT pulse sequences to aid multiplicity determinations. Samples were prepared in solutions of $CDCl_3$ unless otherwise stated.

δ values are expressed as parts per million (p.p.m.) downfield from tetramethylsilane internal standard.

Mass spectra were recorded on a VG 7070E mass spectrometer.

Experimental Procedure:

Synthesis of Methyl 3α,4α,5β-trihydroxycyclohex-1-ene-1-carboxylate (Methyl Shikimate) (26)

HCl gas (dry) was bubbled through a solution of shikimic acid (3g, 17mmol) in dry methanol (40 ml) for 2 hours. The methanol was removed under reduced pressure to give a dark red/ brown oil (6.5g). Column chromatography (ethyl acetate) gave the title compound **26** as a white solid (3.08g, 95%).

R_F 0.33 (ethyl acetate);

m.p. 114 -115.5°C, (Lit.[148] 115- 116.5°C);

νmax (nujol mull) 3315(OH), 1690(C=O), 1630(C=C) cm^{-1};

δ_H (CD_3OD) 2.24 (1H, ddd, J_{gem}18.5, $J_{6\beta,5}$ 6.5, $J_{6\beta,2}$ 2.0, $J_{6\beta,3}$2., Hz, 6β-H), 2.76(1H, ddd, J_{gem} 18.5, $J_{6\alpha,5}$ 6.5, $J_{6\alpha,2}$ 2.0, $J_{6\alpha,3}$ 2 0 Hz, 6α-H), 3.82(3H, s, OMe), 3.78(1H, dd, $J_{5,4}$ 8.0, $J_{5,6\alpha}$ 5.0 Hz, H-5), 3.9(1H, dd, $J_{4,5}$=8.0, $J_{4,3}$ 3.5 Hz, H-4), 4.38(1H, d, $J_{3,2}$ 4.0, $J_{3,4}$ 3.5 Hz, H-3), 6.78 (1H, ddd, $J_{2,3}$ 4.0, $J_{2,6\alpha}$ 2.0, $J_{2,6\beta}$ 2.0 Hz, H-2);

δ_C (CD_3OD) 31.6(C-6), 52.4(OMe), 67(C-5), 68(C-4), 72.3(C-3), 130(C-1), 139(C-2), 169(C=0);

m/z (C. I.) 188 (M^+, 4%).

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-hydroxycyclohex-1-ene-1-carboxylate (86)

Method 1

A solution of methyl shikimate **26** (2g, 10.6mmol) in acetone (100ml) was treated with 2,2-dimethoxy propane (5.54g, 53mmol). A catalytic amount of *p*-toluenesulfonic acid monohydrate was added and the reaction mixture was stirred under a nitrogen atmosphere at room temperature for 24 hours. The solvent was evaporated under reduced pressure to give a brown oil (4.3g). Column chromatrography (petrol-ethyl acetate 1:1) gave the title compound **86** as a very pale yellow oil (2.06g, 85%).

R_F 0.51 (petrol- ethyl acetate 1:1);

ν_{max} (nujol mull) 3435(OH), 1715(C=O), 1630(C=C) cm^{-1};

δ_H (CD_3OD) 1.40(3H, s, Me), 1.44 (3H, s, Me), 2.25(1H, dddd, J_{gem} 17, $J_{6\beta,5}$ 8.5, $J_{6\beta,2}$ 2.0, $J_{6\beta,3}$ 2.0, 6β-H), 2.75(1H, dddd, J_{gem} 17, $J_{6\alpha,5}$ 4.5, 6α-H), 3.23(1H, br s, 5-OH), 3.78(3H, s, OMe), 3.90(1H, m, H-5), 4.11(1H, dd, $J_{4,5}$ 8.0, $J_{4,3}$ 6.5 Hz, H-4), 4.78(1H, br m, H-3), 6.92(1H, ddd, $J_{2,3}$ 3.5, $J_{2,6\alpha}$ 2.0, $J_{2,6\beta}$ 1.0Hz, H-2);

δ_C (CD_3OD) 25.6(Me), 27.8(Me), 29(C-6), 52(OMe), 68.4(C-5), 72(C-4), 78(C-3), 110(CMe_2), 130 (C-1), 134(C-2), 167(C=0).

Method 2

A solution of methyl shikimate **26** (2.5g, 13.3mmol) in 2,2-dimethoxy propane (13.3g, 133mmol), was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate and the reaction stirred under a nitrogen atmosphere at room temperature for fifteen minutes. The solution was neutralized with saturated sodium

bicarbonate, solution extracted with diethyl ether (3x30 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give a brown oil (5.7g). Column chromatography (petrol-ethyl acetate 7:3 - 1:1) gave the title compound as a colourless oil which crystallised on prolonged standing to give a white solid (3.09g, 98%).

m.p. 183-184.5 °C (Lit.[58] 185°C).

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5α-bromocyclohex-1-ene-1-carboxylate (177)

Method 1

A dry flask was charged with **86** (4.31g, 19mmol) and tetrahydrofuran (150ml). Carbon tetrabromide (12.20g, 38mmol) was added, followed by triphenylphosphine (9.72g, 38mmol). The flask was flushed with nitrogen and the reaction mixture was heated at reflux for 6 hours. After cooling to room temperature the organic solvent was evaporated under reduced pressure to give a yellow oil (12.4g). Column chromatrography (petrol-ethyl acetate 4:1) gave the title compound as an off-white solid (438mg, 8%) and diene **195** as a white solid (80mg, 2%).

177

R_F 0.51 (petrol-ethyl acetate 4:1);

m.p. 101-102 °C (Lit.[103] 103 - 105°C);

ν_{max} (nujol mull) 1700 (C=O), 1625 (C=C);

δ_H ($CDCl_3$) 1.39 (3H, s, CCH_3), 1.44 (3H, s, CCH_3), 2.86 (1H, dddd J_{gem} = 16.5, $J_{6\beta\text{-}5}$ = 11.0, 2.75, Hz H-6β), 2.94 (1H, dd, J_{gem} = 16.85, $J_{6\alpha\text{-}5}$ = 5.55 Hz, H-6α), 3.78 (3H, s, CO_2Me), 4.18 (1H, ddd $J_{5,6\beta}$ = 11.0, $J_{5,6\alpha}$ = 5.6, $J_{5,4}$ = 2.0 Hz H-5), 4.58 (1H, d, m J =5.3 Hz, H-4), 4.73 (1H, m, H-3), 6,77(1H, d, m, J 2.4 Hz, H-2);

δ_C ($CDCl_3$) 26.5 (Me), 27.6 (Me), 29.8 (C-6), 43.7 (C-5), 52.4 (OMe), 73.0 (C-4), 76.1 (C-3), 110 (*C* Me_2), 130.4 (C-1), 135.1 (C-2), 166.2 (C=O);

m/z (C.I.) 293 (M^+ 97 (Br^{81})), 291(M^+ 100 (Br^{79})), 277 (40), 275 (41), 235 (52), 233 (50), 153 (90), 137 (59).

195

R_F 0.21 (petrol- ethyl acetate 1:1);

m.p. 53-56 °C (Lit. [34] 54-57 °C);

δ_H ($CDCl_3$) 1.39 (3H, s, Me), 1.41 (3H, s, Me), 3.80 (3H, s, OMe), 4.65 (1H, ddd, $J_{4,3}$ = 9.0, $J_{4,5}$ = 4.0, $J_{4,6}$ = 1.0, Hz, 4-H), 4.81 (1H, dd, $J_{3,4}$ = 9.0, $J_{3,2}$ = 4.0, Hz, 3-H), 6.04 (1H, ddd, $J_{5,6}$ = 10.0, $J_{5,4}$ = 4.0, $J_{5,2}$ = 1.0, Hz, 5-H), 6.54 (1H, br d, $J_{6.5}$ = 10.0, Hz, 6-H), 6.86 (1H, ddd, $J_{2,3}$ = 4.0, $J_{2,6}$ = 1.5, $J_{2,5}$ = 1.0, Hz, 2-H).

Method 2

A dry flask was charged with **86** (860mg, 3.77mmol) and dichloromethane (30ml). Carbon tetrabromide (2.5g, 7.54mmol) was added, followed by triphenylphosphine (1.98g, 7.54mmol). The flask was flushed with nitrogen and the reaction mixture was heated at reflux for 8 hours. After cooling to room temperature the organic solvent was evaporated under reduced pressure to give a yellow oil (5.4g). Column

chromatrography (petrol-ethyl acetate 4:1) gave the title compound as a white solid (99mg, 9%) and diene **195** as (40mg, 5%).

Method 3

A dry flask was charged with **86** (600mg, 2.63mmol) and tetrahydofuran (40ml). Carbon tetrabromide (980mg, 2.89mmol) was added, followed by tributlyphosphine (586mg, 2.89mmol). The flask was flushed with nitrogen and heated at reflux for 6 hours. After cooling to room temperature the organic solvent was evaporated under reduced pressure to give a yellow oil (2.78g). Column chromatrography (petrol-ethyl acetate 4:1) gave the title compound as a white solid (114mg, 25%) and diene **195** (34mg, 6%).

Attempted Synthesis of Methyl 3α,4α-isopropylidenedioxy-5α-bromocyclohex-1-ene-1-carboxylate 177

Method 1

A solution of **86** (325mg, 1.43mmol) in THF (20ml) was treated with a solution of triphenyl phosphine (411mg, 1.57mmol) in THF (10ml) under an atmosphere of nitrogen. Bromine (5ml) was then added dropwise over a fifteen minute period, making sure that the flask temperature was maintained below 55^{o}C. The addition of bromine was stopped when 2 drops persisted in giving the solution an orange tint. T.l.c. analysis of the reaction mixture revealed that no product had been formed and so the reaction mixture was stirred for four hours. Still t.l.c. analysis revealed the presence of starting material and no product and so the reaction mixture was boiled overnight. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Method 2

A solution of **86** (100mg, 4.4mmol) in MeCN (25ml) was treated with a solution of dibromo triphenyl phosphine (370mg, 8.8mmol) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for three hours. T.l.c. analysis of the reaction mixture revealed that no product had been formed. The reaction mixture was then boiled for five hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Method 3

A solution of triphenyl phosphine (185mg, 0.70mmol) in THF (10ml) was added dropwise with stirring to a solution of of N-bromo succinimide (124mg, 0.70mmol) in THF (5ml). To this was added a solution of **86** (146mg, 0.64mmol) in THF (ml). The reaction mixture was then stirred for 4 hours but t.l.c. indicated no conversion. The reaction mixture was then boiled for 5 hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Method 4

A solution of **86** (102mg, 0.45mmol) and phosphorus tribromide (181mg, 0.67mmol, 1.5 eq) in DCM (10ml) was stirred for 16 hours, after which, t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion. The reaction mixture was then boiled for seven hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present. The solution was neutralised with saturated sodium hydrogen carbonate, extracted into ethyl acetate (2x 40ml), dried ($MgSO_4$), filtered and concentrated under reduced

pressure to give an oil which was flash chromatographed to afford the starting material.

Method 5

A solution of lithium bromide (648mg, 7.46mmol) in acetonitrile (20ml) was treated with chlorotrimethylsilane (1.01g, 9.33mmol) with good stirring under an atmosphere of nitrogen. A solution of alcohol **86** (850mg, 3.73mmol) in acetonitrile (10ml) was then added and the reaction mixture was heated under reflux for twelve hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Method 6

A solution of alcohol **86** (206mg, 1.1mmol) in diethyl ether (2ml) was treated with a solution of triphenyl phosphine (575mg, 2.2mmol) in diethyl ether (5ml). A solution of dibromotetrachloroethane (714mg, 2.2mmol) in diethyl ether (1ml) was added slowly with stirring After two hours t.l.c. analysis showed no conversion and so the reaction mixture was heated under reflux overnight. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Method 7

A solution of alcohol **86** (230mg, 1.3mmol) in dichloromethane (2ml) was treated with a solution of triphenyl phosphine (672mg, 2.6mmol) in dichloromethane (1ml). A solution of dibromotetrachloroethane (714mg, 2.6mmol) in dichloromethane (2ml) was added slowly with stirring After one hour t.l.c. analysis showed no conversion

and so the reaction mixture was heated under reflux for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Synthesis of Methyl [1R-(1α,5α,6α)]-5-hydroxy-8-oxo-7,9-dioxabicyclo[4.3.0]-non-2-ene-3-carboxylate (93)[59]

A solution of **26** (517mg, 2.97mmol) in THF (50ml) was heated at reflux under an atmosphere of nitrogen. 1,1'-Carbonyl diimidazole (1.926g, 11.88mmol) was added portion-wise over a period of five hours. The reaction mixture was then boiled for a further 2 hours and then allowed to cool to room temperature. A solution of 6M HCl (15ml) was then added and the reaction mixture was stirred for 2 hours. Most of the THF was removed under reduced pressure to give a pale yellow oil. This was partitioned between ethyl acetate (2x30 ml) and water. The organic extracts were combined, dried ($MgSO_4$) and concentrated in *vacuo* to give an oil that was taken up in ether (60ml) and stirred under reflux for 2 hours. Insoluble material was filtered off and the solvent removed under reduced pressure. Column chromatography (hexane-ethyl acetate 1:1) gave the title compound as a colourless oil that crystallised on standing to give a white solid (456mg, 78%).

R_F 0.36 (hexane-ethyl acetate 1:1);

m.p. 79.5 - 81 °C (Lit. [59] 80 - 82.5°C);

δ_H (acetone - D_6) 2.34 (1H, m, 6β-H), 2.82 (1H, m, 6α-H), 3.76 (3H, s, OMe), 4.12 (1H, dt, J = 7.5, 4.9 Hz, H-3), 4.75 (1H, t, J = 7.5 Hz, H-4), 5.33 (1H, dd, J = 7.5, 3.7 Hz, H-5), 6.87 (1H, m, H-2).

Attempted synthesis of Methyl [1R-(1α,5α,6α)]-5-bromo-8-oxo-7,9-dioxabicyclo[4.3.0]-non-2-ene-3-carboxylate (206)

Method 1

A dry flask was charged with alcohol **93** (132mg, 0.62mmol) and tetrahydrofuran (20ml). Carbon tetrabromide (407mg, 1.23mmol) was added, followed by triphenylphosphine (324mg, 1.23mmol). The flask was flushed with nitrogen and the reaction mixture was heated at reflux for 6 hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**93**, R_F = 0.51) remaining present.

Method 2

A dry flask was charged with alcohol **93** (600mg, 2.63mmol) and tetrahydofuran (40ml). Carbon tetrabromide (980mg, 2.89mmol) was added, followed by tributlyphosphine (586mg, 2.89mmol). The flask was flushed with nitrogen and heated at reflux for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**93**, R_F = 0.51) remaining present.

Method 3

A solution of alcohol **93** (230mg, 1.3mmol) in tetrahydrofuran (2ml) was treated with a solution of triphenyl phosphine (672mg, 2.6mmol) in tetrahydrofuran (1ml). A solution of dibromotetrachloroethane (714mg, 2.6mmol) in tetrahydrofuran (2ml) was added slowly with stirring After one hour t.l.c. analysis showed no conversion and so the reaction mixture was heated under reflux for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**93**, R_F = 0.51) remaining present.

Synthesis of Methyl 2-iodo-2-methyl-3-(toluene-*p*-sulfonyl)propanoate (208)[90]

Iodine (10.19g, 40mmol) and *p*-toluenesulfenic acid, sodium salt hydrate (17.02g, 80mmol) were added to a solution of methylmethacrylate (4g, 40mmol) in freshly distilled methanol ($75cm^3$). The reaction mixture was stirred at 25°C under an atmosphere of nitrogen for 4 hours, after which time t.l.c. (petrol-ethyl acetate 4:1) showed the reaction to be complete. The reaction was poured into distilled water ($750cm^3$) and extracted with ethyl acetate ($2x500cm^3$). The extracts were combined and treated with sodium thiosulphate solution ($500cm^3$, 0.1M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a yellow oil which crystallized on cooling (11.15g, 73%). Prolonged exposure of **208** to light resulted in decomposition to alkene **210**.

208

R_F 0.28 (petrol-ethyl acetate 4:1);

m.p. 131-134 °C (Lit.[90] 127-133°C);

ν_{max} (nujol) 1724 (C=O), 1315, 1280, 1141(SO_2) cm^{-1};

δ_H ($CDCl_3$) 2.44(3H, s, Me), 2.46(3H, s, Ar-Me), 3.80(3H, s, CO_2Me), 3.91(1H, d, J = 14 Hz, 1-H), 4.47(1H, d, J = 14 Hz, 1-H), 7.37(2H, d, J = 8 Hz, Ar-H), 7.77(2H, d, J = 8 Hz, Ar-H);

δ_C ($CDCl_3$) 28.1(Me), 29.0(C-2), 30.1(C-3), 53.6(OMe), 69.0(C-1), 127.8(C-Ar), 130.1(C-Ar), 137.5(C-Ar), 145.2(C-Ar), 171.7(C=O).

210

R_F 0.42 (petrol-ethyl acetate 4:1);

ν_{max} (nujol) 1685 (CO_2Me), 1280, 1295 (SO_2), 1135 (SO_2), 730 cm^{-1};

δ_H ($CDCl_3$) 2.33 (3H, s, Me), 2.45 (3H, s, Ar-Me), 3.79 (3H, s, CO_2Me), 7.22 (1H, s, 1'-H), 7.42 (2H, d, J = 7.9 Hz, Ar-H), 7.82 (2H, d, J = 7.9 Hz, Ar-H);

m/z (C.I.) 255 (MH^+, 100%), 222 (9), 155 (5), 139 (2).

Synthesis of Methyl 2-((toluene-*p*-sulfonyl)methyl) (210) [90,111]

Iodine (6.35g, 25mmol) and *p*-toluenesulfenic acid, sodium salt hydrate (10.70g, 50mmol) were added to a solution of methylmethacrylate (2.67g, 25mmol) in freshly distilled methanol (125cm^3). The reaction mixture was stirred at 25°C under an atmosphere of nitrogen for 24 hours after which time t.l.c. (petrol-ethyl acetate 4:1) showed the reaction to be complete. The reaction was poured into distilled water (750cm^3) and extracted with ethyl acetate (2x 500cm^3). The extracts were combined and treated with sodium thiosulphate solution (500cm^3, 0.1M), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a yellow oil which crystallized on cooling (3.74g, 55%).

Data as above.

Synthesis of Methyl 2-((toluene-*p*-sulfonyl)methyl)propenoate (209) [90]

Method 1

A solution of **210** (10.70g, 28mmol) in dichloromethane (65cm^3) was treated with triethylamine (3.14g, 31mmol) and was heated at reflux under an atmosphere of nitrogen for twenty hours. The mixture was then cooled and washed with 2M hydrochloric acid (75ml), saturated aqueous sodium bicarbonate (50ml), and aqueous sodium thiosulfate (0.5M, 50ml). The combined aqueous washings were back extracted with dichloromethane (3x 30ml), washed with saturated brine (50ml), and the combined organic phases dried ($MgSO_4$). The solvent was then evaporated under reduced pressure to yield a yellow/ orange , viscous oil. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a pale yellow oil (1.06g, 15%) and alkene **210** as pale yellow crystals (4.26g, 60%).

209

R_F 0.25 (petrol-ethyl acetate 4:1);

ν_{max} ($CHCl_3$) 1729 (CO_2Me), 1630, 1598,;

δ_H ($CDCl_3$) 2.44 (3H, s, Ar-Me), 3.59(3H, s, CO_2Me), 4.15(2H, s, 1-H), 5.89(1H, s, 3-H), 6.50(1H, s, 3-H), 7.33(2H, d, J = 8 Hz, Ar-H), 7.72(2H, d, J = 8 Hz,, Ar-H);

δ_C ($CDCl_3$) 21.6(Me), 52.3(OMe), 57.6(C-1), 127.8(C-Ar), 128.7(C-2), 128.9(C-Ar), 129.6 (C-Ar), 133.4(C-3), 135.3(C-Ar), 144.9(C-Ar), 165.3(C=O);

m/z (C.I.) 255(MH^+, 100).

210

Data as above

Method 2

A solution of **208** (10.70g, 28mmol) in dichloromethane (65cm^3) was treated with triethylamine (3.14g, 31mmol) and was heated at reflux under an atmosphere of nitrogen for eight hours. The mixture was then cooled and washed with 2M hydrochloric acid (75ml), saturated aqueous sodium bicarbonate (50ml), and aqueous sodium thiosulfate (0.5M, 50ml). The combined aqueous washings were back extracted with dichloromethane (3x 30ml), washed with saturated brine (50ml), and the combined organic phases dried ($MgSO_4$). The solvent was then evaporated under reduced pressure to yield a yellow/ orange , viscous oil. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a pale yellow oil (5.62g, 79%):

Data as above.

Synthesis of Methyl 2-methylidene-3-tributylstannylpropionate (178)[90]

Method 1

A solution of **209** (150g, .59mmol) in dry toluene (30cm^3) was stirred under an atmosphere of nitrogen. To this was added tributyltin hydride (0.24cm^3,0.89mmol) A catalytic amount of AIBN was added. The reaction mixture was then heated to reflux under a nitrogen atmosphere for $3\,^1/_2$ hours then cooled and concentrated under reduced pressure to yield a milky oil. Column chromatography (petrol-ethyl acetate 99:1 - 9:1) yielded the title compound as a clear , viscous oil which was storred under refrigeration (120mg, 63%):

R_F (petrol) 0.10;

δ_H ($CDCl_3$) 0.80-0.91(12H,m, Bu-H), 1.08-1.36(9H, m, Bu-H), 1.39-1.56(6H,m, Bu-H) 1.98(2H, s this peak shows tin isotopomer satellites , 1-H), 3.73(3H, s,

CO_2Me), 5.29(1H, s this peak shows tin isotopomer satellites , 3-H), 5.81(1H, s this peak shows tin isotopomer satellites , 3-H);

δ_C ($CDCl_3$) 13.5 (C-7), 9.7, 15.0, 27.3 and 28.6 (C-4, C-5, C-6 and C-1), 51.9(OMe), 118.8(C-3), 141.1(C-2), 168.5(C=O);

m/z (FAB(+)) 389 (MH^+,15%), 333(52), 235 (43), 177 (100).

Method 2

A solution of **209** (255mg, 1.00 mmol) in degassed toluene ($30cm^3$) was stirred under an atmosphere of nitrogen. To this was added tributyltin hydride (0.41 cm^3, 1.45mmol) A catalytic amount of tertiary butyl peroxide was added. The reaction mixture was then heated to reflux under a nitrogen atmosphere for $1^1/_2$ hours then cooled and concentrated under reduced pressure to yield a milky oil. Column chromatography (petrol-ethyl acetate 99:1 - 9:1) yielded the title compound as a clear, viscous oil (228mg, 70%).

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonylprop-1-en-3-yl]-cyclo-hex-1-ene-1-carboxylate (173)

Method 1

A solution of 5α-bromo compound **177** (132mg, 0.46mmol) in degassed toluene ($20cm^3$) was treated with the allylstannane **178** (371mg, 0.95mmol). A catalytic amount of AIBN was added, and the reaction mixture was heated, slowly, to reflux under an atmosphere of nitrogen. After six hours at reflux the mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure.

Column chromatography (petrol-ethyl acetate 9:2 to 1:3) gave the title compound as a viscous colourless oil (53mg, 39%) and **179** as a colourless oil (20mg, 15%).:

Combined yield of **173** and **179** = 54%

Ratio 5β -carba chain (**173**) - 5α -carba chain (**179**) = 2.6:1

173

R_F 0. 38(petrol-ethyl acetate 4:1);

ν_{max} 1710 (C=O), 1630 (C=C);

δ_H ($CDCl_3$) 1.39 (3H, s, Me), 1.44 (3H, s, Me), 1.92 (1H, dddd J_{gem} = 17.4, $J_{6\beta\text{-}5}$ = 9.6, 1.75, Hz ,1.75, Hz H-6β), 2.20 (2H, m, 3'-H and 5-H), 2.64 (1H, dd, J_{gem} =17.4, $J_{6\alpha\text{-}5}$ = 3.0, 1.5 Hz, H-6α), 2.73 (1H, dd, J_{gem} =17.4, $J_{3'\text{-}5}$ =8.8, 1.5 Hz, 3'-H), 3.76 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 4.03 (1H, dd $J_{4,5}$ =7.5, $J_{4,3}$ =5.55 Hz, H-4), 4.58 (1H, m H-3), 5.57 (1H, d, $J_{1',3'}$ =1 Hz, 1'-H), 6.25 (1H, d, $J_{1',3'}$ =1 Hz, 1'-H), 6,77 (1H, m, H-2);

δ_C ($CDCl_3$) 25.8 (C-6), 26.1 (Me), 28.2 (Me), 33.8 (C-3'), 35.3 (C-5), 52.3 (OMe), 52.5 (OMe), 71.1 (C-4), 77.1 (C-3), 109.0 (CMe_2), 127.1 (C-1'), 132.6 (C-1), 134.0 (C-2), 138.1 (C-2'), 167.1 (C=O), 167.4 (C=O);

m/z (E.I.) 310 (M^+, 3).

179

R_F 0.41 (hexane-ethyl acetate 4:1);

δ_H ($CDCl_3$) 1.36 (3H, s, Me), 1.37 (3H, s, Me), 2.01 (1H, m, H-6β), 2.51 (1H, m, H-6α), 2.63 (2H, s, 3'-H), 3.76 (3H, s, CO_2Me), 3.78 (3H, s, CO_2Me), 3.86 (1H, m,

H-5), 4.30 (1H, ddd $J_{4,5}$ = 7.9, $J_{4,3}$ = 3.1, $J_{4,2}$ = 2.2 Hz, H-4), 4.58 (1H, m H-3), 5.86 (1H, d, $J_{1',3'}$ = 1 Hz, 1'-H) 6.43 (1H, d, $J_{1',3'}$ = 1 Hz, 1'-H), 6,77 (1H, m, H-2);

δ_C ($CDCl_3$) 25.0 (C-6), 26.4 (Me), 29.5 (Me), 32.0 (C-3'), 40.8 (C-5), 51.5 (OMe), 52.2 (OMe), 71.6 (C-4), 72.1 (C-3), 108.9 (CMe_2), 124.7 (C-1'), 129.9 (C-1), 134.8 (C-2), 135.1 (C-2'), 167.1 (C=O), 167.3 (C=O);

Method 2

A solution of 5α-bromo compound **177** (37mg, 0.13mmol) in degassed toluene ($30cm^3$) was treated with the allylstannane **178** (100mg, 0.26mmol). A catalytic amount of ^tBu-O-O-^tBu was added, and the reaction mixture was heated, slowly, to reflux under an atmosphere of nitrogen. After five hours at reflux the mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure. Column chromatography (petrol-ethyl acetate 9:2 to 1:3) gave the title compound as a viscous colourless oil (16mg,40%), and **179** as a colourless oil (6mg, 15%).

Combined yield of **173** and **179** = 55%

Ratio 5β -carba chain (**173**) - 5α -carba chain (**179**) = 2.65:1

Method 3

A solution of 5β-bromo compound **180** (190mg, 0.65mmol) in degassed toluene ($10cm^3$) was treated with the allylstannane **178** (508mg, 1.3mmol). A catalytic amount of AIBN (12mg) was added, and the reaction mixture was heated, slowly, to reflux under an atmosphere of nitrogen. After three hours heating at reflux the reaction mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure. Column chromatography (hexane-ethyl acetate

4:1) gave the title compound as a viscous colourless oil (67mg, 33%), and **179** as a colourless oil (25mg, 13%).

Combined yield of **173** and **179** = 46%

Ratio 5β -carba chain (**173**) - 5α -carba chain (**179**) = 73:27

Method 4

A solution of 5β-bromo compound **180** (171mg, 0.59mmol) in degassed toluene ($10cm^3$) was treated with the allylstannane **178** (459mg, 1.18mmol). A catalytic amount of ACN (16mg) was added, and the reaction mixture was heated, slowly, to 110°C under an atmosphere of nitrogen. After two hours heating, the mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure. Column chromatography (hexane-ethyl acetate 9:1) gave the title compound as a viscous colourless oil (88mg, 48%), and **179** as a colourless oil (26mg, 14%).

Combined yield of **173** and **179** = 62%

Ratio 5β -carba chain (**173**) - 5α -carba chain (**179**) = 77:23

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-phenylthionoformate-cyclohex-1-ene-1-carboxylate (233)

Method 1

A solution of alcohol **86** (107mg, 0.47mmol) in tetrahydrofuran (10ml), under a nitrogen atmosphere, was cooled to -78°C. Methyl lithium (1.4M, 10.33g, 0.47mmol) was added dropwise over a fifteen minute period. After stirring for fifteen minutes at -78°C, O-phenylchlorothionoformate (97mg, 0.56mmol) was added dropwise. The resulting reaction mixture was allowed to slowly warm to room

temperature over a forty five minute period. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated almost total conversion. The reaction mixture was then stirred at room temperature for three hours. Column chromatography (Petrol-ether 7:3) yielded the title compound as a colourless oil that crystallized on standing (61mg, 35%)

R_F 0.63 (petrol-ethyl acetate 4:1);

m.p. 122 - 124 ^oC;

ν_{max} (nujol mull) 1722 (CO_2Me), 1507, 1289, 1245, 1191, 1152 cm^{-1};

δ_H ($CDCl_3$)1.43 (3H, s, CCH_3), 1.46 (3H, s, CCH_3), 2.60 (1H, dddd, *J*gem = 17, $J6\beta,5$ =4.5, $J6\beta,2$ =1.4, $J6\beta,3$ = 1.4 Hz H-6β), 2.98 (1H, dddd, J_{gem} 17, $J6\alpha,5$ 4.5 Hz H-6α), 3.80 (3H, s, CO_2Me), 4.45 (1H, t, H-5), 4.82 (1H, m, H-4), 5.67 (1H, q, H-3), 6.96 (1H, d,m, H-2), 7.12 (2H, m, Ar-H), 7.29 (1H, m, Ar-H), 7.43 (2H, m, Ar-H):

δ_C ($CDCl_3$) 25.6 (C-6), 26.0 (Me), 27.8 (Me), 52.2 (OMe), 71.9 (C-5), 73.4 (C-4), 79.7 (C-3), 110.2 (CMe_2), 115.3 (C-(Ar-H)), 121.8 (C-(Ar-H)), 126.6 (C-(Ar-H)), 129.1 (C-1), 129.5 (2xC-(Ar-H)), 134.4 (C-2), 153.3 (Ar-1), 166.2 (C=O), 194.3 (C=S):

m/z 365 (MH^+,12%), 307 (20), 211 (18), 153 (100):

(Found: C, 59.7; H, 5.52 $C_{18}H_{20}O_6S$ requires C, 59.33 ; H, 5.53 .%).

Method 2

To a stirred solution of **86** (140mg, 0.6mmol) in dichloromethane (10 cm^3) under an atmosphere of nitrogen, was cooled to 0^oC. Pyridine (58.5mg, 0.74mmol) was added and then O-phenylchlorothionoformate (128mg, 0.74mmol) was added dropwise. The

reaction mixture was kept at 0°C for thirty minutes and was then allowed to warm to room temperature over thirty minutes and was then stirred for three hours. The solvent was removed under reduced pressure to give a dark brown oil. Column chromatography (petrol-ethyl acetate 4:1) yielded the compound as a colourless oil that crystallized on standing (133mg 59%).

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-*p*-tolylthionoformate-cyclohex-1-ene-1-carboxylate (236)

To a stirred solution of **86** (2.1g 9.2mmol) in dichloromethane (30 cm^3) under an atmosphere of nitrogen, was added pyridine (1.46g 18.4mmol) and *p*-tolylchlorothionoformate (3.43g 18.4mmol). After two hours the solvent was removed under reduced pressure to give a dark brown oil. Column chromatography (Petrol-ether 7:3) yielded the title compound as a colourless oil that crystallized on standing (2.96g 85%):

R_F 0.58(petrol-ethylacetate 4:1);

m.p. 118 - 119.5 °C;

ν_{max} (nujol mull) 1709 (CO_2Me), 1514, 1293, 1245 cm^{-1};

δ_H ($CDCl_3$)1.43 (3H, s, CCH_3), 1.45 (3H, s, CCH_3), 2.36 (3H, s, Ar-CH_3), 2.58 (1H, dd, *J*=13, *J*=8, *J*=8 Hz, H-6β), 2.94 (1H, dd, *J*=11, *J*=8, *J*=8 Hz, H-6α), 3.78 (3H, s, CO_2Me), 4.45(1H, t, *J*=6.5, *J*=6.5 Hz H-5), 4.82(1H, dt, H-4), 5.68(1H, m, H-3), 6.74(1H, d,m, H-2), 6.96(2H, m, Ar-H), 7.19(2H, m, Ar-H):

δ_C ($CDCl_3$) 20.9 (Ar-Me), 25.6 (C-6), 26.0 (Me), 27.8 (Me), 52.2 (OMe), 71.9 (C-5), 73.3 (C-4), 79.6 (C-3), 110.3 (CMe_2), 115.0 (C-(Ar-H)), 120.6 (C-(Ar-H)), 121.4

(C-(Ar-H)), 129.1 (C-1), 130.1 (C-(Ar-H)), 134.4 (C-2), 136.4 (Ar-4), 151.2 (Ar-1), 166.3 (C=O), 194.6 (C=S):

m/z (E.I.) 378(M^+,10%):

(Found: C, 60.47; H, 5.9 $C_{19}H_{22}O_6S$ requires C, 60.3 ; H, 5.82 .%).

Attempted synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-trichlorophenyl-thionoformate-cyclohex-1-ene-1-carboxylate (237)

A solution of alcohol **86** (538mg, 2.46mmol) in dichloromethane (5ml) was treated with triethylamine (0.5ml, 3.94mmol) and the reaction mixture stirred under an atmosphere of nitrogen. O-2,4,6-Trichlorophenylchlorothionoformate (1g, 3.53mmol) was added dropwise and the reaction was stirred at room temperature for two hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present. The solvent was removed under reduced pressure and toluene (8ml) was added along with N-hydroxy succinimide (9mg, cat.) and the reaction was heated at 80°C for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Attempted synthesis of Methyl 3α,4α-isopropylidene-dioxy-5β-pentafluoro-phenylthionoformate-cyclohex-1-ene-1-carboxylate (238)

A solution of alcohol **86** (310mg, 1.36mmol) in toluene (10ml) was treated with N-hydroxy succinimide (16mg, 0.14mmol) and the reaction mixture stirred under an

atmosphere of nitrogen. Pyridine (0.11ml, 1.36mmol) and pentafluorophenylchloro-thionoformate (536mg, 2.05mmol) were then added in sequence and the reaction mixture was heated at 80°C for 6 hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material (**86**, R_F = 0.51) remaining present.

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-S-methyldithiocarbonyl-cyclohex-1-ene-1-carboxylate (239)

A solution of alcohol **86** (150mg, 0.66mmol) in tetrahydrofuran (7ml) was treated with a solution of sodium hydride (29mg, mmol) and imidazole (7mg, mmol) in tetrahydrofuran (3ml). The reaction micture was stirred under an atmosphere of nitrogen for two hours and was then treated with carbon disulfide (0.08ml, mmol) dropwise over fifteen minutes. Methyl iodide (0.07ml, mmol) was then added dropwise over fifteen minutes and the reaction mixture stirred for a further thirty minutes. The reaction was quenched with water (10ml), dichloromethane (20ml) was added and the reaction mixture stirred vigorously for 10 minutes. The reaction mixture was then extracted with dichloromethane (3x15ml), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1 to 2:3) afforded the title compound as a colourless oil that crystallised to give colourless prisms after being refridgerated (136mg, 64%).

R_F 0.58 (petrol-ethyl acetate 1:1);

m.p. 104 - 105 °C;

δ_H ($CDCl_3$) 1.41 (3H, s, Me), 1.42 (3H, s, Me), 2.52 (4H, m, SMe, 6β-H), 2.91 (1H, dddd, J_{gem} 17.5, $J_{6\alpha,5}$ 6.0, $J_{6\alpha,2}$ 1.0 $J_{6\alpha,3}$ 1 0 Hz, 6α-H), 3.79 (3H, s, CO_2Me),

4.41 (1H, t, $J_{5,6\alpha}$ = 6, J = 6 Hz, H-5), 4.80 (1H, m, H-3), 6.02 (1H, m, H-4), 6.94 (1H, m, H-2);

δ_C ($CDCl_3$) 19.2 (SMe), 25.7 (C-6), 26.0 (Me), 27.8 (Me), 52.1 (OMe), 71.8 (C-5), 73.2 (C-4), 78.2 (C-3), 110.1 (CMe_2), 129.0 (C-1), 134.3 (C-2), 166.2 (C=O), 215.3 (C=S);

m/z (C. I.) 319 (MH^+, 18%), 153 (100);

(Found: C 49.5 H 5.92 $C_{13}H_{18}O_5S_2$ requires C 49.05 H 5.70.%).

Attempted synthesis of methyl 3α,4α-isopropylidenedioxy-5β-[2-methoxycarbonylprop-1-en-3-yl]-cyclo-hex-1-ene-1-carboxylate (173)

Method 1

A solution of thionocarbonate **233** (227mg, 0.62mmol) in toluene (10ml) was treated with allylstannane **178** (485mg, 1.25mmol). A catalytic amount of AIBN (10mg) was added, and the reaction mixture was heated at 80°C under an atmosphere of nitrogen. After four hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**233**, R_F = 0.63) remaining present. Another quotient of AIBN (10mg) was then added and the reaction mixture was heated at 80°C for a further fifteen hours. Still no product had been formed and so the reaction mixture was then boiled for five hours but t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**233**, R_F = 0.63) remaining present.

Method 2

A solution of thionocarbonate **233** (167mg, 0.46mmol) in benzene (15ml) was treated with allylstannane **178** (357mg, 0.92mmol). A catalytic amount of AIBN (10mg) was added, and the reaction mixture was heated at 80°C under an atmosphere of nitrogen. After four hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**233**, R_F = 0.63) remaining present.

Method 3

A solution of thionocarbonate **236** (mg, mmol) in benzene (ml) was treated with allylstannane **178** (mg, mmol). A catalytic amount of AIBN (mg) was added, and the reaction mixture was heated at 80°C under an atmosphere of nitrogen. After three hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**236**, R_F = 0.58) remaining present.

Method 4

A solution of thionocarbonate **236** (150mg, 0.39mmol) in toluene (10ml) was treated with allylstannane **178** (309mg, 0.79mmol). A catalytic amount of AIBN (15mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After fifteen hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**236**, R_F = 0.58) remaining present.

Method 5

A solution of thionocarbonate **233** (98mg, 0.27mmol) in toluene (12ml) was treated with allylstannane **178** (212mg, 0.54mmol). A catalytic amount of ^{t}Bu-O-O-^{t}Bu (8mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After seven hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**233**, R_F = 0.63) remaining present.

Method 6

A solution of thionocarbonate **236** (68mg, 0.18mmol) in toluene (5ml) was treated with allylstannane **178** (140mg, 0.36mmol). A catalytic amount of ^{t}Bu-O-O-^{t}Bu (5mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After twelve hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no product with starting material (**236**, R_F = 0.58) remaining present.

Method 7

A solution of thionocarbonate **233** (112mg, 0.31mmol) in toluene (ml) was treated with allylstannane **178** (239mg, 0.61mmol). A catalytic amount of ACN (4mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After nine hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no conversion with starting material (**233**, R_F = 0.63) remaining present.

Method 8

A solution of thionocarbonate **236** (235mg, 0.62mmol) in toluene (ml) was treated with allylstannane **178** (484mg, 1.24mmol). A catalytic amount of ACN (5mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After nine hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no product with starting material (**236**, R_F = 0.58) remaining present.

Method 9

A solution of thionocarbonate **236** (266mg, 0.70mmol) in benzene (10ml) was placed in Hanovia photolysis apparatus along with allylstannane **178** (547mg, 1.41mmol). After thoroughly degassing the solution with nitrogen, it was irradiated at 20°C with a 400-W medium pressure mercury lamp with pyrex filter. After four hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated that most of the starting material had reacted to produce at least twenty different close running spots, but none of these spots co-incided with those attributable to the desired products. The reaction was continued for another three hours but t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated that even more products had been formed with some of the starting material (**236**, R_F = 0.58) remaining present.

Method 10

A solution of thionocarbonate **233** (72mg, 0.20mmol) in benzene (9ml) was placed in Hanovia photolysis apparatus along with allylstannane **178** (154mg, 0.40mmol). After thoroughly degassing the solution with nitrogen, it was irradiated at 20°C with a 400-W medium pressure mercury lamp with pyrex filter. After one hour t.l.c.

analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated that most of the starting material had reacted to produce at least nine different close running spots, none of which co-incided with those attributable to the desired products. The reaction was continued for another two hours but t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated that even more products had been formed with some of the starting material (**233**, R_F = 0.61) remaining present.

Method 11

A solution of xanthate **239** (83mg, 0.26mmol) in toluene (10ml) was treated with allylstannane **178** (203mg, 0.52mmol). A catalytic amount of ACN (10mg) was added, and the reaction mixture was heated at reflux under an atmosphere of nitrogen. After two hours t.l.c. analysis (mobile phase = petrol/ ethyl acetate 4:1) indicated no product with starting material remaining present.

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-methanesufonyloxy-cyclohex-1-ene-1-carboxylate (240)

Method 1

A solution of **86** (750mg, 3.3mmol) in dichloromethane (8ml) was treated with pyridine (7.5ml) and cooled to 0^0C. Methanesulfonyl chloride (942mg, 8.2mmol) was added dropwise over a period of ten minutes under an atmosphere of nitrogen. The reaction mixture was then allowed to warm slowly to room temperature and was stirred for three and a half hours. Crushed ice was added, the organic layer was extracted with ether (3x40ml), dried ($MgSO_4$), filtered and removed under reduced pressure to afford a colourless solid. Column chromatography (hexane- ethylacetate 1:1) afforded the title compound as a colourless oil, that was crystallised from chloroform, (684mg, 68%).

R_F 0.52 (hexane-ethyl acetate 1:1);

m.p. 138-140 ^{o}C;

ν_{max} 1720 cm^{-1};

δ_H ($CDCl_3$) 1.41 (3H, s, Me), 1.49 (3H, s, Me), 2.51 (1H, dddd, J_{gem} =17.5, $J_{6\beta,5}$ =8, $J_{6\beta,2}$ =1.5 $J_{6\beta,3}$ =1 5 Hz, 6β-H), 3.0 (1H, dd, J_{gem} =17.5, $J_{6\alpha,5}$ =5 Hz 6α-H), 3.23 (3H, s, SO_2Me), 3.79 (3H, s, CO_2Me), 4.28 (1H, dd, $J_{5,6\beta}$ =8, $J_{5,4}$ =6 Hz, H-5), 4.8 (2H, m, H-3, H-4), 6.97 (1H, m, H-2);

δ_C ($CDCl_3$) 25.7 (Me), 27.5 (Me), 27.7 (C-6), 37.9 (OMe), 71.7 (C-5), 73.9 (C-4), 109.5 (CMe_2), 129.0 (C-1), 134.1 (C-2), 165.6 (C=0);

m/z 307 (MH^+, 27%), 291 (15), 249 (100).

Method 2

A solution of **86** (2.55g, 11.2mmol) in pyridine (10ml) was cooled to 0^0C. Methanesulfonyl chloride (2.2ml) was added dropwise over a period of ten minutes under an atmosphere of nitrogen. The reaction was then allowed to warm slowly to room temperature and was stirred for seventeen hours. Crushed ice was added, the organic layer was extracted with ether (3x30ml), dried ($MgSO_4$), filtered and removed under reduced pressure to afford a colourless oil. Column chromatography (hexane- ethylacetate 1:1) afforded the title compound as a colourless oil (2.72g, 80%).

Method 3

A solution of **86** (3.19g, 14mmol) in dichloromethane (7.5ml) and tetrahydrofuran (7.5ml) was treated with triethylamine (5ml) and cooled to 0^0C. Methanesulfonyl chloride (mg, 35mmol) was added dropwise under an atmosphere of nitrogen, and the

reaction was stirred for ten minutes. Crushed ice was added, the organic layer was extracted with dichloromethane (3x30ml), dried ($MgSO_4$), filtered and removed under reduced pressure. Column chromatography (hexane- ethylacetate 1:1) afforded the title compound 240 as a colourless oil (4.20g, 98%).

Synthesis of Methyl 3α,4α-hydroxy-5β-methanesufonyloxy-cyclohex-1-ene-1-carboxylate (241)

Method 1

A solution of **240** (750mg, 2.45mmol) in tetrahydrofuran (2ml) was treated with water (2ml) and glacial acetic acid (2ml). The reaction mixture was heated to 60^0C for thirty eight hours. Saturated aqueous sodium bicarbonate solution (10ml) was added and the reaction mixture was extracted with ethyl acetate (2x15 ml). The combined washings were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow solid. Column chromatography (ethyl acetate) afforded the title compound as a colourless solid (515mg, 79%).

R_F 0.72 (ethyl acetate);

m.p. 136 - 137 ^oC;

δ_H ($CDCl_3$) 2.36 (1H, dd, J_{gem} = 18, J = 6 Hz, 6β-H), (1H, dd, J_{gem} = ,18 J = 3.5 Hz, 6α-H), 3.20 (3H, s, SO_2Me), 3.65 (3H, s, CO_2Me), 3.89 (1H, dd, H-5), 4.22(1H, s, H-3), 4.80 (1H, q, H-4), 5.30 (2H, dd, 2x OH, exchange with D_2O), 6.71 (1H, s, H-2);

δ_C ($CDCl_3$) 29.5 (C-6), 33.8 (SMe), 53.2 (OMe), 66.4 (C-5), 69.0 (C-4), 78.1 (C-3), 128.0 (C-1), 139.6 (C-2), 167.4 (C=O);

m/z (C.I.) 267 (MH^+, 17), 249 (72), 217 (43), 171 (6), 153 (100).

Method 2

A solution of **240** (627mg, 2.05mmol) in tetrahydrofuran (3ml) was treated with 1N hydrochloric acid (8ml). The reaction mixture was heated to 50^0C for two and half hours. Saturated aqueous sodium bicarbonate solution (15ml) was added and the reaction mixture was extracted with ethyl acetate (2x10ml). The combined washings were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow solid. Column chromatography (ethyl acetate) afforded the title compound as a colourless solid (280mg, 52%).

Method 3

A solution of **240** (820mg, 2.68mmol) in tetrahydrofuran (6ml) was treated with 1N hydrochloric acid (6ml). The reaction mixture was stirred at room temperature for two and half hours. Saturated aqueous sodium bicarbonate solution (20ml) was added and the reaction mixture was extracted with ethyl acetate (2x10 ml). The combined washings were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow solid. Column chromatography (ethyl acetate) afforded the title compound as a colourless solid (579mg, 81%).

Synthesis of Methyl *cis*-3-hydroxy-4,5-oxycyclohex-1-ene-1-carboxylate (120)[59,136]

Method 1

To a solution of triphenylphosphine (302mg, 1.15mmol) and THF (50 cm^3) was added **86** (119mg, 0.58mmol). This was flushed with nitrogen and then cooled to 0°C, DEAD (201mg, 1.15mmol) was then added dropwise with stirring. The mixture was kept at 0°C for 30 minutes after which it was allowed to warm to room

temperature where it stood for 2 hours. The mixture was then concentrated under pressure to give an orange oil that solidified on standing. This was taken up in hot ether, which when cooled gave bis(carboethoxy)hydrazine (190mg). The filtrate was concentrated and after column chromatography (petrol- ethylacetate 4:1) gave the titled product (24mg, 27%) as a pale yellow oil that crystallized on cooling;

R_F 0.45 (hexane-ethyl acetate 1:1);

ν_{max} (nujol) 3550, 3450, 1715, 1655 cm^{-1};

δ_H ($CDCl_3$) 2.44(1H, m, J = 21.2 Hz, H-6β), 2.60(1H, d, , J = 11.1 Hz, OH, exchanges with D_2O), 3.0(1H, m, J =21.2 Hz, H-6α), 3.52(2H, br s, H-4), 3.75(3H,s, OCH_3), 4.55(1 H,m, J=11.1 Hz, H-3), 6.72(1 H, br s, H-2),

bis(carboethoxy)hydrazine

mp 132°C;

δH ($CDCl_3$) 1.28 (6H, t, J = 7.2 Hz, CO_2Et), 4.20 (4H, q, J = 7.2 Hz, CO_2Et), 6.70 (2H, s, 2x NH).

Method 2

To a solution of triphenylphosphine (557mg, 2.12mmol) and THF (50 cm^3) was added **86** (220mg, 1.06mmol). This was flushed with nitrogen and then cooled to 0°C, DEAD (370mg, 2.12mmol) was then added dropwise with stirring. The mixture was kept at 0°C for 30 minutes after which it was allowed to warm to room temperature where it stood for 2 hours. The mixture was then concentrated under pressure to give an orange oil that solidified on standing. The residue was then distilled using a Kugelrohr apparatus. Material distilling up to 130^0C at a pressure of

0.5mm was collected and this was diluted with hot diethyl ether (45ml), which caused N,N-bis(ethoxycarbonyl)hydrazine (190mg) to precipitate. The filtrate was concentrated and after column chromatography (petrol- ethylacetate 4:1) gave the titled product (77mg, 36%) as a pale yellow oil that crystallized on cooling.

Synthesis of Methyl *cis*-3-hydroxy-4,5-oxycyclohex-1-ene-1-carboxylate (120) from Methyl 3α,4α-hydroxy-5β-methanesufonyloxy-cyclohex-1-ene-1-carboxylate (241)

Method 1

A solution of **241** (300mg, 1.13mmol) in tetrahydrofuran (5ml) was treated with potassium tertiary butoxide (140mg, 1.24mmol) and the reaction was stirred under an atmosphere of nitrogen for five hours. Column chromatography (ethyl acetate) gave the title compound as a white crystalline solid (84mg, 43%).

Data as above

Method 2

A solution of **241** (150mg, 0.56mmol) in tetrahydrofuran (8ml), was cooled to 0°C and was treated with potassium tertiary butoxide (70mg, 0.62mmol). The reaction was allowed to warm slowly to room temperature, under an atmosphere of nitrogen, over a three hour period. Concentration under reduced pressure gave a white solid . Column chromatography (ethyl acetate) gave the title compound as a white crystalline solid (50mg, 52%).

Method 3

A solution of **241** (221mg, 0.83mmol) in tetrahydrofuran (14ml), was cooled to -78°C and was treated with potassium tertiary butoxide (102mg, 0.91mmol). The reaction was stirred under an atmosphere of nitrogen for 2 hours and allowed to warm slowly to room temperature. Concentration under reduced pressure gave a white solid. Column chromatography (ethyl acetate) gave the title compound as a white crystalline solid (134mg, 95%).

Synthesis of Methyl 3α,4α-hydroxy-5β-bromocyclohex-1-ene-1-carboxylate (165)

A solution of **120** (900mg, 5.29mmol) in tetrahydrofuran (25ml) was treated with glacial acetic acid (mg, 31.76mmol). Lithium bromide (736mg, 8.46mmol) was then added and the reaction was stirred under an atmosphere of nitrogen for 5 hours. Sodium bicarbonate (mg, mmol) was added and the organic layer was extracted with ethylacetate (3 x 20ml). The organic washings were dried (Na_2SO_4), filtered, and then the solvent was removed under reduced pressure to give a colourless crystalline solid in 97% yield. Column chromatography (hexane-ethyl acetate 1:1) afforded the title compound (1.04g, 78%).

m.p.92 - 94 °C;

ν_{max} (nujol mull) 3315(OH), 1690(C=O), 1630(C=C) cm^{-1};

δ_H ($CDCl_3$) 2.78 (1H, dddd, J_{gem} =18.5, $J_{6\beta,5}$ =8.5, $J_{6\beta,2}$ =1.5 $J_{6\beta,3}$ =1 5 Hz, 6β-H), 2.97 (1H, br s, OH, exchanges with D_2O), 3.09 (1H, br s, OH, exchanges with D_2O), (1H, dddd, J_{gem} =18.5, $J_{6\alpha,5}$ =5, $J_{6\alpha,2}$ =1.5 $J_{6\alpha,3}$ =1 5 Hz, 6α-H), 3.78

(3H, s, CO_2Me), 3.94 (1H, dd, $J_{5,6\beta}$= 8.5 , J = 4 Hz, H-5), 4.38 (1H, m, H-4), 4.62 (1H, br s , H-3), 6.91 (1H, m, H-2);

δ_C (DMSO) 31.7 (C-6), 50.1 (C-5), 51.9 (OMe), 65 (C-4), 69.9 (C-3), 127.4 (C-1), 139.1 (C-2), 165.9 (C=O);

m/z (C.I.) 253(M^+ 97 (Br^{81})), 251(M^+ 100 (Br^{79})), 235 (98), 233 (100), 173 (6), 171 (14), 153 (100), 139 (22), 137 (34);

(Found: C, 38.6; H, 4.54 $C_8H_{11}O_4Br$ requires C, 38.4 ; H, 4.43 .%).

Synthesis of Methyl 3α,4α-hydroxy-5β-iodocyclohex-1-ene-1-carboxylate (242)

A solution of **120** (498mg, 2.92mmol) in tetrahydrofuran (10ml) was treated with glacial acetic acid (0.54ml, 8.79mmol). Lithium iodide (599mg, 4.69mmol) was then added and the reaction was excluded from the light. The reaction was stirred under an atmosphere of nitrogen for eighteen hours. Sodium bicarbonate (72mg) was added and the organic layer was extracted with ethyl acetate (3 x 20ml). The organic washings were washed with sodium thiosulfate (15ml), dried (Na_2SO_4), filtered, and then the solvent was removed under reduced pressure. Column chromatography (hexane-ethyl acetate 1:1) afforded the title compound as a colourless crystalline solid (739mg, 85%).

m.p.134 - 136 ^oC;

ν_{max} (nujol mull) 3337(OH), 1705(C=O), 1640(C=C) cm^{-1};

δ_H ($CDCl_3$) 2.58 (1H, br s, OH, exchanges with D_2O), 2.75 (1H, br s, OH, exchanges with D_2O), 2.94 (H, dd, J_{gem} = 18.5, J= 8.5, Hz, 6β-H), 3.32 (1H, dd,

J_{gem} = 18.5, J= 4.5, Hz, 6α-H), 3.75 (3H, s, CO_2Me), 3.93 (1H, dd, $J_{5,6\beta}$= 8.5, J = 4 Hz, H-5), 4.45 (1H, m, H-4), 4.58 (1H, m, H-3), 6.93 (1H, m, H-2);

δ_C (CD_3OD) 34.2 (C-6), 48.4 (C-5), 50.3 (OMe), 71.1 (C-4), 75.5 (C-3), 130.1 (C-1), 140.1 (C-2), 168.4 (C=O);

m/z (FAB-) 297(M^-, 24), 279 (14), 170 (32);

(Found: C, 31.9; H, 3.75 $C_8H_{11}O_4I$ requires C, 32.22 ; H, 3.72 .%).

Synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-bromocyclohex-1-ene-1-carboxylate (180)

A solution of **165** (495mg, 1.97mmol) in 2,2-dimethoxy propane (2.05g, 19.72mmol), was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate and the reaction stirred under an atmosphere of nitrogen at room temperature for forty five minutes. The solution was neutralized with saturated sodium bicarbonate, extracted with diethyl ether (3x30 ml), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. Column chromatography (petrol-ethyl acetate 1:1) gave the title compound 180 as a colourless solid (488mg, 85%).

δ_H ($CDCl_3$) 1.39 (3H, s, Me), 1.40 (3H, s, Me), 2.78 (1H, dddd, J_{gem} = 18.0, $J_{6\beta,5}$= 7.0, $J_{6\beta,2}$=1, $J_{6\beta,5}$=1, 6β-H), 3.40 (1H, ddd, J_{gem}= 18.0, $J_{6\alpha,5}$= 4.0, $J_{6\alpha,2}$= 1.5 Hz, 6α-H), 3.79 (3H, s, CO_2Me), 4.30 (1H, br dd, $J_{5,6\beta}$=7.0, $J_{5,6\alpha}$=4.0 Hz, H-5), 4.45 (1H, dd, $J_{4,5}$= 6.0, $J_{4,3}$= 5.5 Hz, H-4), 4.78 (1H, s, H-3), 6.92 (1H, m, H-2);

δ_C ($CDCl_3$) 26.4 (Me), 28.2 (Me), 30.1 (C-6), 46.8 (C-5), 52.4 (OMe), 72.1 (C-4), 76.9 (C-3), 110.7 (*C*Me_2), 129.9 (C-1), 134.6 (C-2), 166.4 (C=O);

m/z (C.I.) 292 (M^+ 57 (Br^{81})), 290(M^+ 59 (Br^{79})), 277 (39), 275 (40), 235 (52), 233 (50), 153 (100), 137 (59).

Attempted synthesis of Methyl 3α,4α-isopropylidenedioxy-5β-iodocyclohex-1-ene-1-carboxylate (244)

A solution of **242** (123mg, 0.41mmol) in 2,2-dimethoxy propane (425mg, 4.13mmol), was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate and the reaction stirred under an atmosphere of nitrogen at room temperature for forty five minutes. The solution was neutralized with saturated sodium bicarbonate, extracted with diethyl ether (3x30 ml), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) gave the title compound as a colourless solid (95g, 68%) which underwent rapid decomposition to give a dark brown oil.

Synthesis of Methyl 3α,4α-hydroxy-5β-[2-methoxycarbonylprop-1-en-3-yl]cyclohex-1-ene-1-carboxylate (246)[87]

Method 1

A solution of the acetonide **173** (200mg, 0.65mmol) in THF (3ml) was treated with glacial acetic acid (4ml) and water (3ml), and was heated to 50-60°C under an atmosphere of nitrogen for 35 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution (7ml) and extracted with dichloromethane (2x 5ml). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (petrol-ethylacetate

1:1) yielded the title compound as a colourless solid (60mg, 38%) and the lactone **175** as a colourless solid (25mg, 15%).

246[87]

R_F 0.40 (petrol-ethyl acetate 1:3);

m.p. 119-120 °C;

ν_{max} 3200 (OH), 1720 (CO_2Me), 1620 (C=C);

δ_H ($CDCl_3$) 1.94 (1H, dddd, J_{gem} = 18.0, $J_{6\beta,5}$ = 9.5, $J_{6\beta,2}$ = 2.0 $J_{6\beta,3}$ =1.5 Hz, 6β-H), 2.20 (3H, br s, H-5, 3-OH, 4-OH), 2.31 (1H, dd, J_{gem} = 14.0, $J_{3',5}$ = 8.5 Hz, H-3'), 2.54 (1H, dd, J_{gem} 18.0, $J_{6\alpha,5}$ 5.0 Hz, 6α-H), 2.75 (1H, ddd, J_{gem} = 14.0, $J_{3',5}$ = 4.0, $J_{3',1'}$ = 1.0 Hz, 3'-H), 3.47 (1H, dd, $J_{4,5}$ = 10.0, $J_{4,3}$ = 4.0 Hz, H-4), 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 4.35 (1H, dd, $J_{3,2}$ = 5, $J_{3,4}$ = 4.0 Hz, H-3), 5.67 (1H, d, $J_{1',3'}$ = 1.0 Hz, 1'-H), 6.29 (1H, d, $J_{1',3'}$ = 1.0 Hz, 1'-H), 6.93 (1H, ddd, $J_{2,3}$ = 5.0, $J_{2,6\beta}$ = 2.0, $J_{2,6\alpha}$ = 1.0 Hz, H-2);

δ_C ($CDCl_3$) 28.5 (C-6), 33.5 (C-3'), 34.5 (C-5), 52.0 (OMe), 52.3 (OMe), 65.9 (C-4), 71.7 (C-3), 128.2 (C-1'), 132.6 (C-1), 135.9 (C-2), 137.7 (C-2'), 167.1 (C=O), 168.2 (C=O);

m/z (C.I., NH_3) 288(MNH_4^+, 73), 271 (MH^+19), 253 (100);

(Found: C, 57.55; H, 6.49 $C_{13}H_{18}O_6$ requires C, 57.75 ; H, 6.72 .%).

***Trans*-8α-Hydroxy-6-methoxy-carbonyl-3-methylene-4a,5,8,8a-tetrahydro-4H-benzo[e]pyran-2-one (175)**

R_F 0.49 (petrol-ethyl acetate 1:3);

m.p. 131-133 °C;

ν_{max} (nujol mull) 3480, 3380, 1690, 1610, cm^{-1};

δ_H ($CDCl_3$) 2.0 (2H, br dddd, J_{gem} = 18.0, $J_{6\beta,5}$ = 9.0, $J_{6\beta,2}$ =3.0 $J_{6\beta,3}$ =1.0 Hz, 6β-H and OH), 2.28 (2H, m, H-5 and H-3), 2.83 (2H, m, 6α-H and H-3'), 3.78 (3H, s, CO_2Me), 4.23 (1H, dd, $J_{4,5}$ = 10.5, $J_{4,3}$ =3.0 Hz, H-4), 4.50 (1H, dd, $J_{3,2}$ = 6.0, $J_{3,4}$ =3.0 Hz, H-3), 5.68 (1H, s, H-1'), 6.49 (1H, s, H-1'), 6.95 (1H, dd, $J_{2,3}$ = 6.0, $J_{2,6\beta}$ =3.0 Hz, H-2);

δ_C ($CDCl_3$) 27.8 (C-5), 30.7 (C-6), 34.3 (C-3'), 52.2 (OMe), 63.5 (C-4), 82.3 (C-3), 129.0 (C-1'), 133.0 (C-1), 133.1 (C-2'), 134.2 (C-2), 164.8 (C=O), 166.5 (C=O);

m/z (E.I.) 238(MH^+, 13), 223 (8), 206 (10);

m/z (FAB+) 239 (MH^+, 239.091949 $C_{12}H_{15}O_5$ required 239.091053 , 100%).

Method 2

A solution of **173** (76mg, 0.25mmol) in tetrahydrofuran (15ml) was treated with 1N hydrochloric acid (15ml). The reaction mixture was stirred at room temperature for four hours. Saturated aqueous sodium bicarbonate solution (20ml) was added and the reaction mixture was extracted with ethyl acetate (2x 10ml). The combined washings were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate 1:1) afforded the title compound as a colourless solid (27mg, 46%) and the lactone **175** as a colourless solid (13mg, 21%).

Synthesis of *Trans*-8α-Hydroxy-6-methoxy-carbonyl-3-methylene-4a,5,8,8a-tetrahydro-4H-benzo[e]pyran-2-one (175)

Method 1

A solution of the acetonide **173** (31mg, 0.097mmol) in THF (1ml) was treated with glacial acetic acid (1 ml) and water (1ml), and was heated to 60°C under an atmosphere of nitrogen for 47 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution (5ml) and extracted with dichloromethane (2x 5ml). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (petrol-ethylacetate 1:1) yielded the title compound as a colourless solid (6mg, 30%) and diol **246** as a colourless solid (14mg, 52%).

DATA as above.

Method 2

A solution of the diol **246** (37mg, 0.14mmol) in MeCN (3ml) was treated with potassium carbonate(2mg, 0.007mmol) and was heated to 50°C under an atmosphere of nitrogen for 32 hours. The reaction mixture was diluted with saturated aqueous ammonium chloride solution (5ml) and extracted with dichloromethane (2x 7ml). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (petrol-ethylacetate 3:2) yielded the title compound as a colourless solid (23mg, 63%).

Method 3

A solution of 5β-bromo compound **165** (113mg, 0.45mmol) in degassed toluene ($10cm^3$) was treated with the allylstannane **178** (260mg, 0.67mmol). A catalytic amount of ACN (12mg) was added, and the reaction mixture was heated, at reflux under an atmosphere of nitrogen. After two hours heating, the mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure. Column chromatography (hexane-ethyl acetate 9:1) gave the title compound as a colourless solid (54mg, 51%), and **247** as a colourless solid (20mg, 19%).

247

R_F 0.46 (hexane-ethyl acetate 1:1);

δ_H ($CDCl_3$) 2.01 (1H, dddd, J_{gem} = 18, $J_{6\beta,5}$ = 10, $J_{6\beta,3}$ = 3, $J_{6\beta,2}$ = 3, Hz, 6β-H), 2.27 (1H, m, 5-H), 2.39 (1H, dddd, J_{gem} = 18, $J_{6\alpha,5}$ = 6.5, $J_{6\alpha,2}$ = 2, $J_{6\alpha,3}$ = 2, Hz, 6α-H), 2.61 (1H, m, 3'-H), 2.81 (1H, m, 3'-H), 3.69 (3H, s, OMe), 4.40 (1H, m, 4-H), 4.61 (1H, dt, , Hz, 3-H), 5.65 (1H, m, 1'-H), 6.53 (1H, m, 1'-H), 6.75 (1H, m, 2-H);

δ_C ($CDCl_3$) 24.5 (C-6), 29.4 (C-5), 32.7 (C-3'), 52.04 (OMe), 67.7 (C-4), 77.4 (C-3), 130 (C-1), 131.2 (C-2'),131.6 (C-1'), 137.6 (C-2), 164.9 (C=O), 166.4 (C=O);

m/z (C.I.) 239 (MH^+, 12%), 221 (8);

(Found: C 57.7; H 6.59 $C_{12}H_{14}O_5$ requires C 60.48; H 5.94%).

Method 4

A solution of 5β-iodo compound **242** (120mg, 0.4mmol) in degassed toluene ($10cm^3$) was treated with the allylstannane **178** (181mg, 0.6mmol). A catalytic amount of ACN (10mg) was added, and the reaction mixture was heated, at reflux under an atmosphere of nitrogen. After two hours heating, the mixture was cooled gradually to room temperature and the solvents evaporated under reduced pressure. Column chromatography (hexane-ethyl acetate 9:1) gave the title compound as a colourless solid (94mg, 56%), and **247** as a colourless solid (39mg, 23%).

Attempted synthesis of Methyl 3α,4α-hydroxy-5β-methyl [3,3-difluoro-3-(diethoxyphosphinyl)-2-methyl]propionate-cyclohex-1-ene-1-carboxylate (249)

Method 1

A solution of epoxide **120** (50mg, 0.294mmol) in benzene (7ml) was treated with methyl [3,3-difluoro-3-(diethoxyphosphinyl)-2-hydroxy-2-methyl]propionate **248** (94mg, 0.324mmol) and titanium isopropoxide (0.13ml, 0.441mmol). The reaction mixture was boiled for four hours under an atmosphere of nitrogen. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated no conversion with starting material remaining present.

Method 2

Synthesis of Isopropyl 3α,4α-hydroxy-5β-isopropylcyclohex-1-ene-1-carboxylate (250)

A solution of epoxide **120**(89mg, 0.52mmol) in benzene (7ml) was treated with methyl [3,3-difluoro-3-(diethoxyphosphinyl)-2-hydroxy-2-methyl]propionate **248** (305mg, 1.05mmol) and titanium isopropoxide (298mg, 1.05mmol). The reaction mixture was stirred at room temperature for three hours. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated the presence of a new spot with starting material (**86**, R_F = 0.51) remaining present. The reaction was left to stir overnight, but t.l.c. analysis indicated that most of the starting material was still present. The benzene was removed under reduced pressure and the reaction mixture was then taken up in ether (10ml). 5% H_2SO_4 (5ml) was added and the reaction mixture was stirred vigourously for one hour until two distict layers were visible. The organic layer was then extracted with dichloromethane (2x5ml) and dried ($MgSO_4$). Column chromatography (petrol/ethyl acetate 1:1- 3:2) yielded isopropyl 3α,4α-hydroxy-5β-isopropylcyclohex-1-ene-1-carboxylate **250** as a colourless oil (15mg, 11%).

ν_{max} ($CHCl_3$) 3436, 2978, 2931, 1705, 1648, 1261, 1096 cm^{-1};

δ_H ($CDCl_3$) 1.21 (12H, ddt, *J*= 6Hz, *J*= 2Hz, ^{i}OPr Me), 1.74 (1H, br s, 4-OH), 2.12 (1H, dddd, J_{gem} = 17.5, $J_{6\beta,5}$ = 9, $J_{6\beta,2}$ = 1.0, $J_{6\beta,3}$ = 1.0, Hz, 6β-H), 2.86 (1H, d, $J_{6\alpha,5}$ 4Hz, 6α-H), 2.95 (1H, br d, 3-OH), 3.64 (1H, dd, $J_{5,6\beta}$ = 9, $J_{4,5}$ = 4, Hz, 5-H), 3.77 (2H, m, ^{i}OPr C-H), 4.5 (1H, br t, $J_{4,5}$ = 4, $J_{4,3}$ = 4, Hz, 4-H), 5.07 (1H, m, 3-H), 6.88 (1H, m, 2-H);

δ_C ($CDCl_3$) 21.8 (2x ^{i}Pr Me), 22.2 (^{i}Pr Me), 23.4 (^{i}Pr Me), 30.1 (C-6), 65.8 (^{i}Pr CH), 68.4 (^{i}Pr C-H), 70.6 (C-5), 71.6 (C-4), 71.8 (C-3), 131.5 (C-1), 134.8 (C-2), 165.8 (C=O);

m/z (C.I.) 258 (M^+, 3%), 171 (48), 128 (10);

(Found: C 59.0 H 8.57 $C_{13}H_{22}O_5$ requires C 60.45 H 8.58.%).

Method 3

Synthesis of Methyl 3α,4α-hydroxy-5β-fluorocyclohex-1-ene-1-carboxylate (251)

A solution of epoxide **120** (70mg, 0.41mmol) in DCM (4ml) was treated with methyl[3,3-difluoro-3-(diethoxyphosphinyl)-2-hydroxy-2-methyl]-propionate[141] **248** (131mg, 0.45mmol). The reaction mixture was cooled to 0°C and boron trifluoride etherate (5ml, 0.1 equv.) was added dropwise over five minutes. The reaction mixture was then stirred at 0°C for one hour. T.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated that both starting materials remained but a new spot had been formed. The reaction mixture was then stirred for a further three hours at 0°C but t.l.c. analysis (mobile phase = petrol/ ethyl acetate 1:1) indicated that starting material was still present. The reaction mixture was then allowed to warm to room temperature and was stirred overnight but t.l.c. analysis indicated that the reaction had not proceeded any further. Column chromatography (petrol-ethyl acetate 1:1 - 1:3) gave **251** as a colourless oil (4mg, 5%).

δ_H ($CDCl_3$) 2.45 (1H, m, 6β-H), 2.82 (1H, m, 6α-H), 3.33 (2H, br s, 2x OH), 3.75 (3H, s, CO_2Me), 4.92 (1H, m, H-5), 4.45 (1H, br s H-3), 4.85 (1H, d m, H-4), 6.77 (1H, br s, H-2);

δ_F ($CDCl_3$, 400) -194 to -193.7 (m);

δ_C ($CDCl_3$, 400) 28.4 (C-6), 52.2 (OMe), 66.0 (C-5), 68.1 (C-4), 89.6 (C-3), 128.7 (C-1), 136.4 (C-2), 166.5 (C=O);

m/z (C. I.) 191 (MH^+, 65%), 173 (100);

(Found: C 50.9 H 5.84 $C_8H_{11}O_4F$ requires C 50.53, H 5.83%).

Synthesis of Methyl 3α,4α-hydroxy-5β-fluorocyclohex-1-ene-1-carboxylate (251)

A solution of epoxide **120** (99mg, mmol) in DCM (2ml) was treated dropwise with HF.pyridine (1ml, mmol) under an atmosphere of nitrogen. After stirring for ninety minutes the reaction was quenched with aqueous calcium carbonate (250mg in 9ml water). The organic layer was then extracted with ethyl acetate (4x 10ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. Column chromatography (petrol-ethyl acetate 1:9) afforded the title compound as a colourless oil (47mg, 43%). Data as above.

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